Faller, Robert B. - Medicaid

From: Heineman, Susan M [susan.m.heineman@pfizer.com]
Sent: Thursday, August 06, 2009 5:05 PM
To: Faller, Robert B. - Medicaid
Cc: Eide, Tamara J. - Medicaid
Subject: Testimony/points of consideration for next P&T meeting: Alzheimer agents, NSAIDs, Glaucoma agents, Atypical Antipsychotics

Dear P&T Committee,

I appreciate the opportunity to provide concise testimony on new information at the next P&T meeting or at a minimum have the Committee consider my comments below. I have asked Pfizer Medical Information to email the Executive Summaries for Geodon, Celebrex, and Xalatan which contain supporting information.

Here are the key points I would like you to consider when reviewing the classes on August 21, 2009:

Alzheimer agents (I do not feel I need to provide testimony, but please consider these points):
1. Donepezil (Aricept) is the only agent approved for mild, moderate, and severe Alzheimer's Disease
2. 95% of Medicaid patients prescribed an acetylcholinesterase inhibitor are prescribed donepezil (based on publicly available CMS data for 4th quarter, 2008)

3. Of the patients on donepezil, approximately 80% are receiving 10mg and 20% are on 5 mg. Both doses are therapeutic doses.

NSAIDS:
Please consider
1. changing COX-2 PA to allow patients on low-dose aspirin to receive celecoxib for FDA approved indications - for supporting material, please refer to "Celebrex Use with Cardioprotective Aspirin" in the submitted Celebrex Executive Summary

Glaucoma agents:
Please consider the following about latanoprost (Xalatan):
1. provides consistently high persistency rates when compared with other ocular glaucoma treatments (refer to Xalatan Executive Summary)

2. has the lowest rates of hyperemia (Provider Synergy Review). Hyperemia is an adverse effect that most negatively affects medication adherence in this group of medications

3. is prescribed in 50% or Idaho Medicaid recipients on a prostaglandin analog glaucoma agent (based on publicly available CMS data for 4th quarter, 2008)

4. has the Xal-Ease delivery system to ensure drop is accurately placed in the eye and allows patient to get more drops out of the bottle

5. I would like to the opportunity to dispel negative claims about the BAK preservative if that is a concern of the committee

Atypical Antipsychotics:
Please consider for following
1. Open Access - As Schizophrenia and Acute Bipolar are challenging conditions, please consider no access restrictions, or very few, for this class of medications and allow the choice to be made between provider and patient.

2. Weight/metabolic effects? - ziprasidone (Geodon) has a favorable metabolic profile and a neutral effect on weight
3. QT concerns? - In phase I and II of the CATIE trial, there were no significant differences between ziprasidone and any

of the other antipsychotics in mean change in QTc interval (olanzapine, 1.2 msec; quetiapine, 5.9 msec; risperidone, 0.2 msec, perphenazine, 1.4 msec; ziprasidone, 1.3 msec). (refer to Geodon Executive Summary).

4. Drug interactions: Ziprasidone is unlikely to cause clinically important drug interactions mediated by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (refer to Geodon Executive Summary)

Respectfully submitted,

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Worldwide Pharmaceuticals Operations

August 03, 2009

Tami Eide, PharmD
Idaho Dept. of Health and Welfare
PO Box 83720
Boise, ID 83720

Dear Dr. Eide

Your Medical Outcomes Specialist, Susan Heineman, has referred to Medical Information your request for information regarding Celebrex® (celecoxib). Pfizer Inc is pleased to provide you with the following information in response to your specific request. PLEASE NOTE that this information is intended only for the specific person who has requested information about a specific Pfizer Inc product. IF YOU DID NOT SPECIFICALLY REQUEST THE INFORMATION THAT IS INCLUDED, PLEASE DISCARD IT AND CALL 1-800-438-1985 TO REPORT THIS TO US.

The enclosed document contains relevant clinical and economic data for your review. Please keep in mind that this information was prepared with the understanding that it should not be disclosed to anyone other than those who in the course of their job responsibilities require access to the Executive Summary.

Carefully consider the potential benefits and risks of Celebrex and other treatment options before deciding to use Celebrex. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. Celebrex is indicated: 1) for relief of the signs and symptoms of osteoarthritis; 2) for relief of the signs and symptoms of rheumatoid arthritis in adults; 3) for relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older; 4) for the relief of signs and symptoms of ankylosing spondylitis; 5) for the management of acute pain in adults; 6) for the treatment of primary dysmenorrhea; and 7) to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celebrex treatment will persist after Celebrex is discontinued. The efficacy and safety of Celebrex treatment in patients with FAP beyond six months have not been studied.

I hope this information is helpful. Thank you for your interest in Pfizer. Please contact Pfizer at 1-800-438-1985 to report an Adverse Event or if you have any other questions regarding Pfizer products. Licensed healthcare professionals may also log on to www.pfizermedicalinformation.com. Please take a few moments to let us know how we are meeting your needs by completing our survey via the web at http://survey.pfizermedicalinformation.com using the reference number listed below the signature at the end of this letter.

Sincerely,

Michael S. Rocco, PharmD
Director
Pfizer U.S. Medical Information

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Encl.

Celebrex®
(celecoxib)

Executive Summary
04-May-2009

CELEBREX® (celecoxib)
EXECUTIVE SUMMARY
May 4, 2009

Since its launch in the U.S. in 1999, Celebrex continues to provide proven efficacy across a range of indications, has a similar cardiovascular (CV) profile to nonselective nonsteroidal anti-inflammatory drugs (ns-NSAIDs), and has an extensively reviewed gastrointestinal (GI) safety and tolerability profile. Celebrex can also be used with low dose aspirin (ASA), unlike many ns-NSAIDs where concomitant ASA use is generally not recommended, and can be continued in the perioperative setting in osteoarthritis (OA), rheumatoid arthritis (RA), and acute pain patients.

CLINICAL BACKGROUND AND BURDEN OF ILLNESS

Pain is one of the major causes of disability in people with arthritis. Over time, arthritis can severely restrict a patient's ability to function, leading to physiologic and psychosocial impairment, a less independent lifestyle, and a reduced overall quality of life. In fact, arthritis is the leading cause of chronic disability among people >18 years of age. The goals of arthritis management, therefore, are to decrease pain and minimize loss of function.

Arthritis management places an enormous medical and economic burden on society, given that nearly 1 of 8 people in the U.S. suffers from this condition. The prevalence of arthritis is growing. It is projected that by 2020 there will be a 57% increase in the number of patients with this condition since 1990, from 37.9 million to 59.4 million. Furthermore, this condition is not limited to the elderly; nearly one quarter of the U.S. population between the ages of 45 and 65 suffers from some form of arthritis.

CLINICAL SAFETY

Cardiovascular (CV) Safety

Boxed Warning For Potential CV Risk:

- Celebrex may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk. Celebrex is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.[1]

Celebrex versus Placebo CV Adverse Event (AE) Data from Clinical Trials:

- Safety information from a long-term investigational colorectal adenoma prevention trial, Adenoma Prevention with celecoxib (APC), demonstrated a statistically significant dose-related increase in serious CV thrombotic events (nonfatal heart attack, nonfatal stroke and death from CV causes, combined) with Celebrex doses of 200 mg twice daily ([*bid*]; 2 times the approved OA dose; risk ratio=2.6; 95% CI: 1.1-6.1) and 400 mg *bid* (4 times the approved OA dose; risk ratio=3.4; 95% CI: 1.5-7.9) compared with placebo over 3 years of treatment. Safety information from a second long-term investigational study, Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) demonstrated no statistically significant increased risk for the same CV endpoint with Celebrex 400 mg once daily (*qd*) compared with placebo in patients with a history of colorectal adenomas. An analysis of the combined data from both trials showed a nearly 2-fold higher risk for the composite of nonfatal heart attack, nonfatal stroke and death from CV causes, combined, in patients treated with Celebrex 200 mg *bid* or 400 mg *bid* or 400 mg *qd* compared with placebo-treated patients. These results are consistent with the current warnings on CV risk in the Celebrex Package Insert.[2,3,4]
- Safety data for up to 3 years from the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) did not show an increase in serious CV thrombotic events (nonfatal heart attack, nonfatal stroke and death from CV causes, combined) with Celebrex 200 mg *bid* compared to placebo, nor did it show an increase in

the broader composite CV endpoint of nonfatal heart attack, nonfatal stroke, death from CV causes, congestive heart failure, or transient ischemic attack (TIA) for Celebrex 200 mg *bid* versus placebo.[5]

- A pooled analysis of 6 randomized, double-blind, placebo-controlled trials of patients with conditions *other than* arthritis found a significant trend for increased CV risk progressing from placebo to 400 mg *qd* to 200 mg *bid* to 400 mg *bid*. Additionally, an increase in the overall event rate was seen across baseline risk categories regardless of Celebrex use, with a doubling of risk between the low and moderate CV risk groups and a further doubling between the moderate and high CV risk groups. With all doses pooled, the data suggested an interaction between Celebrex use and baseline risk with respect to outcomes with patients in the highest risk group demonstrating the greatest risk of Celebrex-related AEs.[6]

Celebrex versus ns-NSAIDs CV AE Data from Clinical, Epidemiologic, and Observational Studies:

- CV data collected in individual randomized, controlled trials in arthritis patients have also shown that there are no differences in the incidence of CV thromboembolic events or cardiorenal AEs between Celebrex and ns-NSAID groups.[1,7,8,9] Specifically, CV AE data from the prospective Celebrex Long-Term Arthritis Safety Study (CLASS) did not show an increase in serious CV thrombotic events (MI, pulmonary embolism, deep vein thrombosis, unstable angina, TIA, and ischemic cerebrovascular accident) for Celebrex 400 mg *bid* versus diclofenac 75 mg *bid* and ibuprofen 800 mg three times daily (*tid*).[7,8]
- In CLASS, a significantly lower percentage of patients taking Celebrex 400 mg *bid* (4x the FDA approved dose for OA) experienced new-onset and aggravated hypertension and edema versus ibuprofen (800 mg *tid*).[10]
- Meta-analyses of randomized, controlled trials have generally demonstrated that Celebrex is not associated with an increased risk of serious CV thromboembolic events or cardiorenal events compared with ns-NSAIDs.[11,12,13,14]
- Substantial information on CV and cardiorenal risk of COX-2 inhibitors and ns-NSAIDs can be found in various epidemiologic and observational studies.[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35]
- Results from a population-based cohort analysis of electronic medical records did not show any difference in the hazard rates of incident hypertension between Celebrex and ns-NSAID users.[36]
- Celebrex has not been associated with an increased risk of CV AEs in elderly patients aged ≥65 years.[16,18,28,37]

Celebrex Use with Cardioprotective Aspirin:

- In a randomized, double-blind, placebo-controlled study, Celebrex was well tolerated in healthy patients who received concomitant ASA and did not alter the antiplatelet activity of ASA.[38]
- Celebrex can be used with low-dose ASA[1], unlike many ns-NSAIDs in which concomitant ASA use is not generally recommended (i.e. ibuprofen, naproxen, diclofenac, meloxicam, and nabumetone).[39,40,41,42,43]
- Celebrex has no effect on platelet aggregation responses in healthy volunteers[1], unlike naproxen, which significantly inhibits platelet function.[44] Celebrex has no effect on the antiplatelet effect of ASA in healthy patients,[38] whereas ibuprofen can affect the antiplatelet activity of ASA.[45]

Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) Study:

- Pfizer is supporting the on-going PRECISION study, which will prospectively assess the relative safety of ibuprofen, naproxen and Celebrex for at least 18 months, at doses commonly used by OA and RA patients and provide greater understanding of the relative CV safety of NSAIDs. This study will enroll ~20,000 OA and RA patients with or at increased risk for CV disease. This is the first prospective study evaluating the CV safety of Celebrex. The study is being conducted by the Cleveland Clinic.

Gastrointestinal (GI) Safety

Boxed Warning for GI Risk:

- NSAIDs, including Celebrex, cause an increased risk of serious GI AEs including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.[1]

Celebrex versus ns-NSAIDs on Upper GI Complications in Clinical Trials:

- In CLASS, Celebrex 400 mg *bid* (4x the FDA approved dose for OA) demonstrated similar rates of upper GI ulcer complications (the primary outcome measure of ulcer complications; defined as perforation, gastric outlet obstruction, and bleeding) compared with ns-NSAIDs at their standard prescription doses (ibuprofen 800 mg *tid* and diclofenac 75 mg *bid*) at 6 months and over the entire study period, ≤15 months (p=0.09 at 6 months; p=0. 45 at ≤15 months). However, Celebrex did demonstrate a significantly lower rate of the number of symptomatic ulcers combined with ulcer complications (secondary outcome measure) versus ns-NSAIDs combined, at 6 months and over the entire study period, ≤15 months (p=0.02 at 6 months; p=0.04 at ≤15 months).[1,46]
- In CLASS, for patients not taking ASA, the incidences of ulcer complications and ulcer complications plus symptomatic ulcers were significantly greater in the ibuprofen group versus the Celebrex group (p=0.005 for ulcer complications; p<0.001 for ulcer complications plus symptomatic ulcers). Those patients on Celebrex and concomitant low-dose ASA experienced 4-fold higher rates of complicated ulcers compared to those not on ASA.[1,47]
- In SUCCESS I, a randomized, double-blind trial in >13,000 OA patients treated for >12 weeks, Celebrex 100 mg *bid* or 200 mg *bid* was associated with a significantly reduced risk of upper GI complications (perforation, obstruction, and bleeding) compared with ns-NSAIDs (naproxen 500 mg *bid* and diclofenac 50 mg *bid* groups combined).[48]
- In patients with high GI risk, the use of Celebrex has been found to be comparable to an ns-NSAID plus a proton pump inhibitor (PPI) in reducing the risk of recurrent ulcer bleeding.[49,50,51]
- In a study of patients with previous upper GI bleeding (those at highest risk for additional upper GI bleeding), treatment with Celebrex 200 mg *bid* plus esomeprazole 20 mg *bid* was more effective than Celebrex alone for prevention of ulcer bleeding in these patients.[52]
- Observational studies have shown Celebrex use has a reduced risk of upper GI bleeding when compared to ns-NSAIDs.[53,54,55]

Celebrex versus ns-NSAIDs on GI Tolerability in Clinical Trials:

- In controlled clinical trials, a lower percentage of Celebrex patients experienced abdominal pain, dyspepsia, or nausea versus ibuprofen or naproxen patients.[1] In CLASS, a lower percentage of Celebrex treated patients had dyspepsia versus patients taking diclofenac.[56] In SUCCESS-1, a significantly lower percentage of Celebrex patients discontinued therapy due to abdominal pain or dyspepsia compared with patients taking naproxen.[57] The AEs of abdominal pain, dyspepsia, and nausea, which indicate tolerability, may not correlate with GI bleeding or other GI complications.
- Celebrex has been associated with better GI tolerability compared with ns-NSAIDs; fewer patients receiving Celebrex have experienced upper GI AEs compared with patients who received ns-NSAIDs in a number of randomized, controlled trials and a meta-analysis.[14,48,58,59,60,61,62]
- In a pooled analysis of GI AEs including >23,000 OA, RA or ankylosing spondylitis (AS) patients, Celebrex patients (treated with 200 mg *qd* and 400 mg *qd*) experienced a significantly lower incidence of the 5 most common GI AEs (abdominal pain, dyspepsia, diarrhea, flatulence and nausea) versus ibuprofen (800 mg *tid*), and naproxen (500 mg *bid*) patients. Celebrex patients also experienced a lower incidence of discontinuation due to any GI AE versus ibuprofen and naproxen.[63,64]

Celebrex versus ns-NSAIDs on Blood Loss:

- Regardless of ASA use, the CLASS study at 9 months demonstrated that the incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients receiving Celebrex 400 mg *bid* compared with patients on either diclofenac 75 mg *bid* or ibuprofen 800 mg *tid* (0.5%, 1.3%, and 1.9%, respectively).[1,46]

Celebrex versus ns-NSAIDs Endoscopic Studies:

- In controlled clinical trials, Celebrex 50 mg *bid* to 400 mg *bid* demonstrated a statistically significant lower incidence of endoscopically detected gastroduodenal ulcers compared with the ns-NSAIDs, naproxen, in two 12-week trials and diclofenac, at 6 months. The correlation between findings of short-term endoscopic studies with Celebrex and the relative incidence of clinically significant serious upper GI events with long-term use has not been established.[1]
- In 2 prospective, randomized, double-blind, placebo-controlled trials in healthy adult patients, significantly fewer patients who received Celebrex plus low-dose ASA (81 or 325 mg) developed endoscopically detected upper GI ulcers compared with patients who received naproxen plus low-dose ASA after 1 week.[65,66] The correlation between findings of short-term endoscopic studies with Celebrex and the relative incidence of clinically significant serious upper GI events with long-term use has not been established.[1]
- In 2 prospective, randomized, double-blind, placebo-controlled studies in healthy adult patients, significantly fewer patients who received Celebrex developed gastric or small bowel mucosal breaks (detected by video capsule endoscopy) compared with patients who received naproxen plus omeprazole or ibuprofen plus omeprazole after 2 weeks.[67,68]
- In older patients (≥65 years), Celebrex was associated with the development of fewer endoscopic ulcers compared with ns-NSAIDs,[69] and with an improved GI tolerability, with patients experiencing less dyspepsia, abdominal pain, and nausea and vomiting.[70]

Safety in Special Populations

- Dose adjustment in the elderly is not generally necessary; however, for patients <50 kg (<110 lbs) in body weight, therapy should be initiated at the lowest recommended dose. Area under the curve (AUC) is approximately 40% higher in Blacks compared to Caucasians.[1]
- In pediatric patients, the oral clearance (unadjusted for body weight) of Celebrex increases less than proportionally to increasing body weight, with 10 kg (22 lb) and 25 kg (55 lb) patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg (154 lb) adult RA patient. Not studied in juvenile rheumatoid arthritis (JRA) patients aged <2 years.[1]
- Relative to healthy patients, AUC increased 40% in patients with mild and 180% in patients with moderate hepatic impairment. Use in patients with severe hepatic impairment is not recommended.[1]
- AUC is 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than in patients with normal renal function.[1]
- Hepatic metabolism via cytochrome P_{450} (CYP) 2C9 is the primary route of Celebrex elimination. Known or suspected P_{450} 2C9 poor metabolizers based on a previous history should be administered Celebrex with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.[1]
- There are no studies in pregnant women. Celebrex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

CLINICAL EFFICACY

Relief of Signs and Symptoms of Osteoarthritis:

- Celebrex has been studied in clinical trials with >25,000 patients in 21 randomized double-blind OA clinical trials of 2-12 weeks duration.[62] Overall, Celebrex showed superior efficacy compared with placebo and comparable efficacy compared with ns-NSAIDs, in the treatment of the signs and symptoms of hip and knee OA, as measured by standard OA efficacy assessments.[1,71] In addition, Celebrex has also been studied in clinical trials with >10,000 patients in 6 randomized, double-blind OA/RA trials of 12-52 weeks duration with similar efficacy results.[62]
- Celebrex was more efficacious than placebo and acetaminophen (APAP) in the treatment of the signs and symptoms of hip and knee OA. Furthermore, more patients preferred Celebrex treatment to APAP treatment.[72]

Relief of Signs and Symptoms of Rheumatoid Arthritis:

- Celebrex has been studied in clinical trials with >3,000 patients in 4 randomized, double-blind RA clinical trials of 4-24 weeks duration.[62] Similar to results from OA trials, Celebrex demonstrated superior efficacy in the treatment of symptomatic RA compared with placebo. Comparable efficacy in RA patients has been demonstrated between Celebrex 100 mg *bid* and 200 mg *bid* and naproxen 500 mg *bid*[73] and between Celebrex 200 mg *bid* and diclofenac 75 mg *bid*.[74]

Relief of Signs and Symptoms of JRA in Patients 2 Years and Older:

- Celebrex suspension formulation was found to have similar efficacy to naproxen suspension formulation in a 12-week study comparing the efficacy and safety in pediatric patients with JRA.[1,75,76] The dose for children ≥2 years and 10-25 kg (22-55 lbs) is 50 mg *bid*, and for those >25 kg (>55 lbs) is 100 mg *bid*. A 50 mg capsule is available; for patients that cannot swallow the capsule, the contents of the capsule may be emptied onto a level teaspoon of applesauce and ingested immediately with water.[1]

Management of Acute Pain in Adults and Treatment of Primary Dysmenorrhea:

- Pivotal studies evaluating the management of acute pain in >3,000 patients were conducted in post-orthopedic surgery, post-general surgery, post-oral surgery, and primary dysmenorrhea pain models.[77] These studies demonstrated that Celebrex provided significantly greater analgesic efficacy than placebo in terms of onset, magnitude, and/or duration of analgesia in patients with moderate to severe pain.[1,77,78] Multiple doses of Celebrex were more efficacious than multiple doses of hydrocodone 10 mg/APAP 1000 mg in 2 pivotal studies of patients with acute pain following orthopedic surgery.[77,78]
- Celebrex can be used perioperatively because it has the same effect on platelets as placebo and does not affect bleeding time, unlike naproxen and ibuprofen.[44,45]
- Celebrex significantly reduced post-arthroscopic knee surgery pain at rest and at flexion in 2 randomized, double-blind, placebo-controlled trials at 8, 10 and 12 hours post-surgery.[79,80]
- In a 36-hour randomized, double-blind, placebo-controlled trial, Celebrex, when used as part of a multimodal pain management strategy with hydrocodone/APAP, provided significant reductions in postsurgical knee pain compared to hydrocodone/APAP alone.[79]
- In a prospective, randomized, double-blind, placebo-controlled study evaluating the effect of short-term postoperative administration of Celebrex on pain management following laparoscopic surgery, Celebrex reduced mean pain scores and the need for analgesics at 24 and 48 hours postoperatively. Patient satisfaction with their postoperative pain management was also significantly higher in the Celebrex group and bowel function recovered on average 1 day earlier and patients resumed activities of daily living 2 days earlier in the Celebrex group.[81]
- Celebrex has demonstrated to be similarly efficacious to ibuprofen and naproxen for the treatment of pain related to ankle sprain[82,83] and similarly efficacious to naproxen for the treatment of acute shoulder pain.[84,85]
- Celebrex has been studied in numerous other acute pain models, including post-surgical dental pain,[86] gynecological surgery,[87,88] acute pharyngitis[89] and low back pain.[90]
- Results from 2 pivotal primary dysmenorrhea studies demonstrate that Celebrex is efficacious (based on onset, magnitude, and duration of analgesia) and safe in the treatment of primary dysmenorrhea. The mean values of the primary measures of efficacy for this indication, the Sum of Pain Intensity Difference at 8 hours (SPID[8]) and Total Pain Relief at 8 hours (TOTPAR[8]), were statistically significantly better for Celebrex and naproxen than those observed for placebo across both studies.[91,92]

Relief of Signs and Symptoms of Ankylosing Spondylitis:

- Celebrex has been studied in clinical trials with >1600 patients in 4 randomized, double-blind AS studies of 6-12 weeks duration.[93] Doses of Celebrex 200-400 mg daily (given either *qd* or *bid*) were shown to be statistically superior to placebo and comparable to naproxen 500 mg *bid*, diclofenac 50 mg *tid* or 75 mg SR *bid*, or ketoprofen 100 mg *bid* in treating the signs and symptoms associated with AS.[1,93,94,95]

To Reduce the Number of Adenomatous Colorectal Polyps in Familial Adenomatous Polyposis (FAP):

- In a randomized, double-blind, placebo controlled 26-week trial, Celebrex 400 mg *bid* significantly reduced the number of polyps and overall colorectal polyp burden compared with placebo.[1,96]

COST ANALYSIS

Health-Related Quality of Life and Outcomes Studies

- Celebrex improved health-related quality of life (HRQL) in patients with OA, RA, and AS as measured by HRQL tools such as the Short-Form 36 (SF-36), WOMAC OA Index, and specific AS HRQL assessments. Celebrex improved bodily pain, and physical, emotional, and social functioning in these patient groups.[97,98,99,100]
- Retrospective and observational studies have demonstrated that users of Celebrex were more likely to stay on therapy for longer and were less likely to switch medications than those patients taking ns-NSAIDs.[101,102,103]
- Celebrex has been found to reduce GI healthcare resource utilization compared with ns-NSAIDs. Celebrex was associated with a reduction in the number of hospitalizations for UGI events (including hemorrhage), intensive care unit hospitalizations, physician and specialist visits, and blood transfusions.[104,105] Similar findings were observed in patients aged ≥65 years.[106,107]

Economic Analysis

Several U.S. and non-U.S. cost-effectiveness analyses relating to Celebrex have been published in recent years. Generally, the findings from these analyses have been mixed reflecting the differences in model structure properties, cost-effectiveness indicators, and relative drug prices between each. The economic model by Loyd is the first to employ an exclusively OA population, to account for reductions in drug prices with the loss of patents, to extrapolate probabilities based on long-term evidence from the literature, and to test, within sensitivity analyses, the effect of: increasing age on GI risk, the length of the analytic horizon, and importantly in the current environment, the effects of CV thromboembolic risk.[108]

The discounted total cost to the third-party payer per average-risk, older OA patient over her/his lifetime was approximately $14,000 for those taking Celebrex and $10,000 for those taking ns-NSAIDs. However, this estimate does not assume that UGI risks rise with advancing age. In the same cohort, Celebrex users cost about $31,000 per Quality-Adjusted Life Year (QALY) gained compared with ns-NSAID users. Taking into account advancing age and cumulative GI risk, Celebrex users cost about $19,000 more per QALY gained compared with ns-NSAID in average risk patients. In such OA patients at average risk using Celebrex or ns-NSAIDs over a lifetime, assuming differential CV thrombotic risks, the incremental cost of Celebrex per QALY gained is no more than approximately $40,000. These results indicate that Celebrex is cost-effective versus ns-NSAIDs for older (>60 years) OA patients with average baseline UGI risks considering a cost-effectiveness threshold of about $60,000.[108] Furthermore, Celebrex has good economic value under various assumptions regarding serious CV thromboembolic risks.

CONCLUSIONS

Clinical data confirm that Celebrex continues to provide proven efficacy across a range of indications. Celebrex has a similar CV profile to prescription ns-NSAIDs and an extensively reviewed GI safety and favorable tolerability profile compared to ns-NSAIDs. Celebrex can also be used with low dose ASA, unlike many ns-NSAIDs where concomitant ASA use is generally not recommended. Celebrex can be used in the perioperative setting to treat OA, RA, and acute pain. Meta-analyses of randomized, controlled trials have generally demonstrated that Celebrex was not associated with an increased risk of serious CV events compared with ns-NSAIDs. Observational studies, with greater numbers of patients, confirm these findings of a similar CV profile for Celebrex compared to ns-NSAIDs. There are also data demonstrating an improved HRQL with Celebrex, as shown by a number of quality of life assessments, and also a reduction in healthcare resource utilization. Furthermore, evidence exists to show that

Celebrex users are more likely to remain on treatment for longer and to switch therapies less frequently than users of ns-NSAIDs, which in itself has important economic implications. The clinical and safety data for Celebrex are supported by the economic model by Loyd, which demonstrated cost-effectiveness of Celebrex in OA patients with moderate GI risk.

Arthritis is a serious and painful condition and is the leading cause of disability in the U.S. For many patients with arthritis, not treating their pain is not an option. Therefore, all patients should discuss their personal health profile with their doctor in order to determine the most appropriate treatment option.

For patients who need prescription NSAID therapy, the evidence presented provides a clear rationale for the inclusion of Celebrex as an important treatment option for patients in pain.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of Celebrex and other treatment options before deciding to use Celebrex. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Celebrex is indicated:
1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) For relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients 2 years and older.

4) For the relief of signs and symptoms of ankylosing spondylitis.

5) For the management of acute pain in adults.

6) For the treatment of primary dysmenorrhea.

7) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celebrex treatment will persist after Celebrex is discontinued. The efficacy and safety of Celebrex treatment in patients with FAP beyond six months have not been studied.

Refs.

1. Celebrex® (celecoxib capsules) Package Insert.
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3. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006;355:885-895.
4. Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006;114:1028-1035.
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August 03, 2009

Tami Eide, PharmD
Idaho Dept. of Health and Welfare
PO Box 83720
Boise, ID 83720

Dear Dr. Eide

Your Medical Outcomes Specialist, Susan Heineman, has referred to Medical Information your request for information regarding Geodon® (ziprasidone hydrochloride capsules or ziprasidone mesylate injection). Pfizer Inc is pleased to provide you with the following information in response to your specific request. PLEASE NOTE that this information is intended only for the specific person who has requested information about a specific Pfizer Inc product. IF YOU DID NOT SPECIFICALLY REQUEST THE INFORMATION THAT IS INCLUDED, PLEASE DISCARD IT AND CALL 1-800-438-1985 TO REPORT THIS TO US.

The enclosed document contains relevant clinical and economic data for your review. Please keep in mind that this information was prepared with the understanding that it should not be disclosed to anyone other than those who in the course of their job responsibilities require access to the Executive Summary.

Geodon (ziprasidone hydrochloride) is indicated for the treatment of schizophrenia as well as for acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. Geodon for Injection (ziprasidone mesylate) is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

I hope this information is helpful. Thank you for your interest in Pfizer. Please contact Pfizer at 1-800-438-1985 to report an Adverse Event or if you have any other questions regarding Pfizer products. Licensed healthcare professionals may also log on to www.pfizermedicalinformation.com. Please take a few moments to let us know how we are meeting your needs by completing our survey via the web at http://survey.pfizermedicalinformation.com using the reference number listed below the signature at the end of this letter.

Sincerely,

Michael S. Rocco, PharmD
Director
Pfizer U.S. Medical Information

SANTIAGOA / 11474588

Encl.

GEODON®
(ziprasidone HCl)
Capsules

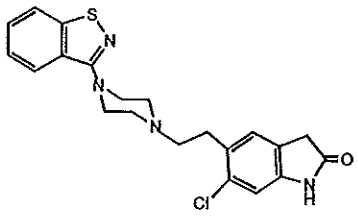
GEODON®
(ziprasidone mesylate)
for Injection
FOR IM USE ONLY

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Geodon (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

DESCRIPTION

GEODON® is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration and as GEODON for Injection (ziprasidone mesylate) for intramuscular injection. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions - see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α_1-

adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Oral Pharmacokinetics
Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics
Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

Special Populations

Age and Gender Effects - In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Race - No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking - Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

Renal Impairment - Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg BID dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Hepatic Impairment - As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg BID for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in $AUC_{0\text{-}12}$ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Drug-Drug Interactions

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly

administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

Schizophrenia
The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one long-term (52-week) trial. All trials were in inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:
(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg BID dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for

52 weeks. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.

There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

Bipolar Mania
The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder with an acute manic or mixed episode with or without psychotic features.

Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression – Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in bipolar mania follow:
(1) In a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg BID on Day 1 and 80 mg BID on Day 2. Titration within the range of 40-80 mg BID (in 20 mg BID increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg.

(2) In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg BID on Day 1. Titration within the range of 40-80 mg BID (in 20 mg BID increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Acute Agitation in Schizophrenic Patients
The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed

consent for participation in pre-marketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:
(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

INDICATIONS AND USAGE

Schizophrenia
Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**). Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known (see **WARNINGS**).

The efficacy of oral ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, GEODON was demonstrated to delay the time to and rate of relapse. The physician who elects to use GEODON for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania
Ziprasidone is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see **CLINICAL**

PHARMACOLOGY).

The effectiveness of ziprasidone for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ziprasidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Acute Agitation in Schizophrenic Patients
Ziprasidone intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**). Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

CONTRAINDICATIONS

QT Prolongation
Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**).

Hypersensitivity
Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Geodon (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).

QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval (see CONTRAINDICATIONS, and see Drug Interactions under PRECAUTIONS). Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS).

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg BID).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) (see ADVERSE REACTIONS; Other Events Observed During Post-marketing Use).

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products (see INDICATIONS AND USAGE).

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome

(NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for

continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies, which did not include GEODON, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because GEODON was not marketed at the time these studies were performed, it is not known if GEODON is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General
Leukopenia, Neutropenia and Agranulocytosis – *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia and agranulocytosis have been reported temporally related to antipsychotic agents.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of Geodon should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue Geodon and have their WBC followed until recovery.

Rash - In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Orthostatic Hypotension - Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures - During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Dysphagia - Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).**

Hyperprolactinemia - As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and

tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment - Somnolence was a commonly reported adverse event in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism - One case of priapism was reported in the premarketing database. While the relationship of the event to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation - Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide - The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness - Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under **CLINICAL PHARMACOLOGY, Special Populations**) is limited.

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QTc Prolongation** under **WARNINGS** and **Orthostatic Hypotension** under **PRECAUTIONS**).

Information for Patients
Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

Laboratory Tests
Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before proceeding with treatment. Patients who are

started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec (see **WARNINGS).**

Drug Interactions
Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

Pharmacodynamic Interactions

(1) Ziprasidone should not be used with any drug that prolongs the QT interval **(see CONTRAINDICATIONS).**
(2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.
(3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.
(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions
The Effect of Other Drugs on Ziprasidone
Carbamazepine - Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole - Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine - Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid - The coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs
In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Lithium - Ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of

450 mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives - Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan - Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** under **PRECAUTIONS, General**).

Mutagenesis - Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility - Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

Pregnancy - Pregnancy Category C - In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased

incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery - The effect of ziprasidone on labor and delivery in humans is unknown.

Nursing Mothers - It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

Pediatric Use - The safety and effectiveness of ziprasidone in pediatric patients have not been established.

Geriatric Use - Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

Premarketing experience

The premarketing development program for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

The premarketing development program for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse events during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone
The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone
Schizophrenia--Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**).

Bipolar Mania--Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials--The most commonly observed adverse events associated with the use of ziprasidone (incidence of 5% or greater)

and not observed at an equivalent incidence among placebo-treated patients (ziprasidone incidence at least twice that for placebo) are shown in Tables 1 and 2.

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 4- and 6-Week Trials -- SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Somnolence	14	7
Respiratory Tract Infection	8	3

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 3-Week Trials -- BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=279)	Placebo (N=136)
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Abnormal Vision	6	3
Asthenia	6	2
Vomiting	5	2

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 10% in bipolar mania trials.

** Dizziness includes the adverse event terms dizziness and lightheadedness.

Adverse Events Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those events that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials -- SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=702)	Placebo (N=273)

Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Chest Pain	3	2
Cardiovascular		
Tachycardia	2	1
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Nervous		
Extrapyramidal Symptoms*	14	8
Somnolence	14	7
Akathisia	8	7
Dizziness**	8	6
Respiratory		
Respiratory Tract Infection	8	3
Rhinitis	4	2
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 5% in schizophrenia trials.

** Dizziness includes the adverse event terms dizziness and lightheadedness.

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those events that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 4. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials – BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=279)	Placebo (N=136)
Body as a Whole		
Headache	18	17

Asthenia	6	2
Accidental Injury	4	1
Cardiovascular		
Hypertension	3	2
Digestive		
Nausea	10	7
Diarrhea	5	4
Dry Mouth	5	4
Vomiting	5	2
Increased Salivation	4	0
Tongue Edema	3	1
Dysphagia	2	0
Musculoskeletal		
Myalgia	2	0
Nervous		
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Anxiety	5	4
Hypesthesia	2	1
Speech Disorder	2	0
Respiratory		
Pharyngitis	3	1
Dyspnea	2	1
Skin and Appendages		
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	6	3

* Extrapyramidal Symptoms includes the following adverse event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 10% in bipolar mania trials.

** Dizziness includes the adverse event terms dizziness and lightheadedness.

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of this demographic factor.

Dose Dependency of Adverse Events in Short-Term, Fixed-Dose, Placebo-Controlled Trials
An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS) - The incidence of reported EPS (which included the adverse event terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating

Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Dystonia - *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Vital Sign Changes - Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain - The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6- week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes - Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Events Observed During the Premarketing Evaluation of Oral Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident.

Cardiovascular System: *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis.

Digestive System: *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena.

Endocrine: *Rare:* hypothyroidism, hyperthyroidism, thyroiditis.

Hemic and Lymphatic System: *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia.

Metabolic and Nutritional Disorders: *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis.

Musculoskeletal System: *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy.

Nervous System: *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.

Respiratory System: *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus.

Skin and Appendages: *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash.

Special Senses: *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.

Urogenital System: *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction,

anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage.

Adverse Findings Observed in Trials of Intramuscular Ziprasidone

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

TABLE 5. Treatment-Emergent Adverse Event Incidence In Short-Term Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Event		
Body System/Adverse Event	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0

Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

Other Events Observed During Post-marketing Use

Adverse event reports not listed above that have been received since market introduction include rare occurrences of the following (no causal relationship with ziprasidone has been established): *Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors - see **WARNINGS**); *Digestive System Disorders:* Swollen tongue; *Nervous System Disorders:* Facial droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class - Ziprasidone is not a controlled substance.

Physical and Psychological Dependence - Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience - In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3240 mg, the

only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

In post-marketing use, adverse events reported in association with ziprasidone overdose generally included extrapyramidal symptoms, somnolence, tremor, and anxiety.

Management of Overdosage - In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

When deciding among the alternative treatments available for schizophrenia, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**).

Initial Treatment

GEODON® Capsules should be administered at an initial daily dose of 20 mg BID with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 to 100 mg BID in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 to 80 mg BID, but results were not consistent. An increase to a dose greater than 80 mg BID is not generally recommended. The safety of doses above 100 mg BID has not been systematically evaluated in clinical trials.

Maintenance Treatment
While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID (see **CLINICAL PHARMACOLOGY**). No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania
Initial Treatment
Oral ziprasidone should be administered at an initial daily dose of 40 mg BID with food. The dose should then be increased to 60 mg or 80 mg BID on the second day of treatment and subsequently adjusted on the basis of toleration and efficacy within the range 40-80 mg BID. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg (see **CLINICAL PHARMACOLOGY**).

Maintenance Treatment
There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of mania with ziprasidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone in such longer-term treatment (i.e., beyond 3 weeks).

Intramuscular Administration for Acute Agitation in Schizophrenia
The recommended dose is 10 to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

Dosing in Special Populations
Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

Intramuscular: Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Dosing adjustments are not required on the basis of gender or race.

Preparation for Administration
GEODON® for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

GEODON ® Capsules are differentiated by capsule color/size and are imprinted in black ink with "Pfizer" and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON® Capsules			
Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	NDC-0049-3960-60	396
Bottles of 60	40	NDC-0049-3970-60	397
Bottles of 60	60	NDC-0049-3980-60	398
Bottles of 60	80	NDC-0049-3990-60	399
Unit dose/80	20	NDC-0049-3960-41	396
Unit dose/80	40	NDC-0049-3970-41	397
Unit dose/80	60	NDC-0049-3980-41	398
Unit dose/80	80	NDC-0049-3990-41	399

Storage and Handling — GEODON® Capsules should be stored at 25°C (77°F); excursions permitted

to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

GEODON® for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions - see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

GEODON® for Injection		
Package	Concentration	NDC Code
Single Use Vials	20 mg/mL	NDC-0049-3920-83

Storage and Handling - GEODON® for Injection should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature] in dry form. Protect from light. Following reconstitution, GEODON for Injection can be stored, when protected from light, for up to 24 hours at 15°-30°C (59°-86°F) or up to 7 days refrigerated, 2°-8°C (36°-46°F).

Rx only

Distributed by

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PATIENT SUMMARY OF INFORMATION ABOUT

GEODON® Capsules

(ziprasidone HCl)

Information for patients taking GEODON or their caregivers

This summary contains important information about GEODON. It is not meant to take the place of your doctor's instructions. Read this information carefully before you take GEODON. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about GEODON.

What Is GEODON?

GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder.

Who Should Take GEODON?

Only your doctor can know if GEODON is right for you. GEODON may be prescribed for you if you have schizophrenia or acute manic or mixed episodes associated with bipolar disorder.

Symptoms of schizophrenia may include:

- hearing voices, seeing things, or sensing things that are not there (hallucinations)
- beliefs that are not true (delusions)
- unusual suspiciousness (paranoia)
- becoming withdrawn from family and friends

Symptoms of manic or mixed episodes of bipolar disorder may include:

- extremely high or irritable mood
- increased energy, activity, and restlessness
- racing thoughts or talking very fast
- easily distracted
- little need for sleep

If you show a response to GEODON, your symptoms may improve. If you continue to take GEODON there is less chance of your symptoms returning. Do not stop taking the capsules even when you feel better without first discussing it with your doctor.

It is also important to remember that GEODON capsules should be taken with food.

What is the most important safety information I should know about GEODON?

GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with a diagnosis of psychosis related to dementia treated with antipsychotics are at an increased risk of death when compared to patients who are treated with placebo (a sugar pill).

GEODON is an effective drug to treat the symptoms of schizophrenia and the manic or mixed episodes of bipolar disorder. However, one potential side effect is that it may change the way the electrical current in your heart works more than some other drugs. The change is small and it is not known whether this will be harmful, but some other drugs that cause this kind of change have in rare cases caused dangerous heart rhythm abnormalities. Because of this, GEODON should be used only after your doctor has considered this risk for GEODON against the risks and benefits of other medications available for treating schizophrenia or bipolar manic and mixed episodes.

Your risk of dangerous changes in heart rhythm can be increased if you are taking certain other medicines and if you already have certain abnormal heart conditions. Therefore, it is important to tell your doctor about any other medicines that you take, including non-prescription medicines, supplements, and herbal medicines. You must also tell your doctor about any heart problems you have or have had.

Who should NOT take GEODON?

Elderly patients with a diagnosis of psychosis related to dementia. GEODON is not approved for the treatment of these patients.

Anything that can increase the chance of a heart rhythm abnormality should be avoided. Therefore, do not take GEODON if:

- You have certain heart diseases, for example, long QT syndrome, a recent heart attack, severe heart failure, or certain irregularities of heart rhythm (discuss the specifics with your doctor)

- You are currently taking medications that should not be taken in combination with ziprasidone, for example, dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.

What To Tell Your Doctor Before You Start GEODON

Only your doctor can decide if GEODON is right for you. Before you start GEODON, be sure to tell your doctor if you:

- have had any problem with the way your heart beats or any heart related illness or disease
- any family history of heart disease, including recent heart attack
- have had any problem with fainting or dizziness
- are taking or have recently taken any prescription medicines

- are taking any over-the-counter medicines you can buy without a prescription, including natural/herbal remedies
- have had any problems with your liver
- are pregnant, might be pregnant, or plan to get pregnant
- are breast feeding
- are allergic to any medicines
- have ever had an allergic reaction to ziprasidone or any of the other ingredients of GEODON capsules. Ask your doctor or pharmacist for a list of these ingredients
- have low levels of potassium or magnesium in your blood

Your doctor may want you to get additional laboratory tests to see if GEODON is an appropriate treatment for you.

GEODON And Other Medicines

There are some medications that may be unsafe to use when taking GEODON, and there are some medicines that can affect how well GEODON works. While you are on GEODON, check with your doctor before starting any new prescription or over-the-counter medications, including natural/herbal remedies.

How To Take GEODON

- Take GEODON only as directed by your doctor.
- Swallow the capsules whole.
- Take GEODON capsules with food.
- It is best to take GEODON at the same time each day.
- GEODON may take a few weeks to work. It is important to be patient.
- Do not change your dose or stop taking your medicine without your doctor's approval.
- Remember to keep taking your capsules, even when you feel better.

Possible Side Effects

Because these problems could mean you're having a heart rhythm abnormality, contact your doctor ***IMMEDIATELY*** if you:

- Faint or lose consciousness
- Feel a change in the way that your heart beats (palpitations)

Common side effects of GEODON include the following and should also be discussed with your doctor if they occur:

- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea

- Restlessness
- Rash
- Increased cough / runny nose

If you develop any side effects that concern you, talk with your doctor. It is particularly important to tell your doctor if you have diarrhea, vomiting, or another illness that can cause you to lose fluids. Your doctor may want to check your blood to make sure that you have the right amount of important salts after such illnesses.

For a list of all side effects that have been reported, ask your doctor or pharmacist for the GEODON Professional Package Insert.

What To Do For An Overdose

In case of an overdose, call your doctor or poison control center right away or go to the nearest emergency room.

Other Important Safety Information

A serious condition called neuroleptic malignant syndrome (NMS) can occur with all antipsychotic medications including GEODON. Signs of NMS include very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure. NMS is a rare but serious side effect that could be fatal. Therefore, tell your doctor if you experience any of these signs.

Adverse events related to high blood sugar (hyperglycemia), sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Dizziness caused by a drop in your blood pressure may occur with GEODON, especially when you first start taking this medication or when the dose is increased. If this happens, be careful not to stand up too quickly, and talk to your doctor about the problem.

Before taking GEODON, tell your doctor if you are pregnant or plan on becoming pregnant. It is advised that you don't breast feed an infant if you are taking GEODON.

Because GEODON can cause sleepiness, be careful when operating machinery or driving a motor vehicle.

Since medications of the same drug class as GEODON may interfere with the ability of the body to adjust to heat, it is best to avoid situations involving high temperature or humidity.

It is best to avoid consuming alcoholic beverages while taking GEODON.

Call your doctor ***immediately*** if you take more than the amount of GEODON prescribed by your doctor.

GEODON has not been shown to be safe or effective in the treatment of children and teenagers under the age of 18 years old.

Keep GEODON and all medicines out of the reach of children.

How To Store GEODON

Store GEODON capsules at room temperature (59°-86°F or 15°-30°C).

For More Information About GEODON

This sheet is only a summary. GEODON is a prescription medicine and only your doctor can decide if it is right for you. If you have any questions or want more information about GEODON, talk with your doctor or pharmacist. You can also visit www.geodon.com.

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Geodon®
(ziprasidone HCl)

Executive Summary
17-Sep-2008

Geodon® (ziprasidone HCl)
EXECUTIVE SUMMARY
September 17, 2008

Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. Geodon® is available as Geodon® Capsules (ziprasidone hydrochloride) and as Geodon® for Injection (ziprasidone mesylate).[1] Geodon® Capsules are indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with Bipolar Disorder, with or without psychotic features.[1] Geodon® intramuscular (IM) injection is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need IM antipsychotic medication for rapid control of the agitation.[1]
The full Geodon® Dossier provides a comprehensive review of epidemiologic, clinical efficacy, safety, and cost-effectiveness data supporting the use of ziprasidone. This Executive Summary presents an overview of the information provided in the Dossier, including burden of illness, clinical efficacy, safety, health related quality of life, economic benefits, and overall value.

BURDEN OF ILLNESS

Schizophrenia affects approximately 2.4 million US adults and accounts for an estimated $63 billion in direct and indirect costs (2002 dollars).[2,3] Bipolar disorder affects an additional 5.7 million US adults and accounts for an additional $45 billion in costs (1991 dollars).[4,5] Common to both of these disorders is the significant rate of comorbid medical conditions including cardiovascular disease, obesity, diabetes, HIV infection, respiratory conditions, and hepatitis, which translates into significant elevations in mortality and reductions in lifespan.[2,6,7] Estimates suggest that schizophrenia and bipolar patients die decades earlier (13-30 years depending on state) than the general population and that coronary heart disease and other diabetes and cardiovascular conditions are the leading causes of mortality in this population.[7] Furthermore, comorbid schizophrenia and diabetes are associated with significantly greater healthcare resource use and costs of care than diabetes or schizophrenia alone.[8] Comprehensive management of both the physical and psychiatric aspects of this disease is critical to lowering the overall burden of these diseases on patients, health care systems, and society.

CLINICAL EFFICACY

Schizophrenia

Positive and negative symptoms of schizophrenia

Ziprasidone is efficacious in patients with schizophrenia in placebo-controlled trials.[1,9,10,11]

- In a 4-week, placebo-controlled trial (N=139) comparing two fixed doses of ziprasidone (20 and 60 mg BID) with placebo, the 60 mg BID dose was superior to placebo on the BPRS total score and the Clinical Global Impression Severity of Illness (CGI-S) score.[1,9]

- In a 6-week, placebo-controlled trial (N=302) comparing two fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were superior to placebo on the BPRS total score, the Brief Psychiatric Rating Scale (BPRS) psychosis cluster, the CGI severity score and the Positive and Negative Syndrome Scale (PANSS) total and negative subscale scores.[1,10]

- In a 6-week, placebo-controlled trial (N=419) comparing three fixed doses of ziprasidone (20, 60, and 100 mg BID) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI-S score.[1]

- A study was conducted of chronic, symptomatically stable schizophrenic inpatients (N=294) randomized to three fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse," defined as a CGI improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.[1,11]

Ziprasidone is shown to be as efficacious as other atypical antipsychotics in the treatment of positive and negative symptoms of schizophrenia.[12,13,14,15,16]

- In a 6-week, randomized, double-blind trial, ziprasidone and olanzapine demonstrated comparable improvement in all efficacy measures (PANSS total and subscales, BPRS total, CGI-S, CGI improvement scale, and Calgary Depression Scale for Schizophrenia).[12] Continued comparable improvements in efficacy measures were observed in the 6-month extension of this trial.[13]

- In an 8-week, randomized, double-blind trial, ziprasidone displayed improvement in psychotic symptoms comparable to risperidone with significant reductions in PANSS total mean scores, PANSS negative subscale scores, BPRS-derived (BPRSd) total and core items, CGI-S scale, and Global Assessment of Functioning [GAF] scores (all $P<0.001$ vs baseline).[14] Although both treatment groups resulted in significant improvements from baseline in PANSS, CGI-S, and MADRS scores in the 44-week continuation study of responders, a greater proportion of ziprasidone-treated patients experienced clinically significant decreases (≥7%) in body weight compared with risperidone.[15]

- In a randomized, double-blind, 4-week study, both ziprasidone and aripiprazole were efficacious in improving global illness severity and overall psychopathology with robust effect sizes.[16]

Ziprasidone is shown to be more efficacious than the conventional antipsychotic haloperidol in the treatment of negative symptoms of schizophrenia.[17]

- In a 28-week, randomized, double-blind trial, more ziprasidone-treated patients were classified as negative symptom responders (≥20% decrease on the PANSS negative subscale) compared with haloperidol (48% vs 33%, respectively; $P<0.05$).[17]

Relapse prevention and remission

Ziprasidone is efficacious in preventing relapse and improving remission rates.[11,18,19,20]

- A study was conducted in chronic, symptomatically stable schizophrenic inpatients (N=294) randomized to three fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse," defined as a CGI improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.[11]

- In a 6-month, follow-up, observational study, after patients were switched from their previous treatment with risperidone, olanzapine, or conventional antipsychotics to ziprasidone, more than 85% experienced sustained clinical remission.[18]

- In a 40-week, randomized, double-blind core study followed by a 3-year double-blind continuation study, the proportion of patients in remission in the final 6 months was significantly higher in the ziprasidone twice daily (BID) group and the combined ziprasidone BID and QD groups vs haloperidol (40%, 38%, and 23%, respectively; $P<0.05$).[19]

- In a 6-month, double-blind, controlled extension trial, significantly more patients treated with ziprasidone 80-160 mg/day were in remission (based on BPRS criteria) at study endpoint compared with patients treated with olanzapine 5-15 mg/day (80% vs 46%, respectively; $P = 0.022$).[20]

Depression in Schizophrenia

Ziprasidone significantly improves symptoms of depression in patients with schizophrenia.[21,22]

- Depressive symptoms (total and total modified MADRS scores) improved in patients with schizophrenia or schizoaffective disorder in 1-year extensions of three 6-week open-label (core) studies in which stable outpatients were switched to flexible-dose ziprasidone (40-160 mg/day) from conventional antipsychotics, olanzapine, or risperidone.[21]

- Pooled data from two similarly designed, 6-week, randomized, double-blind, placebo-controlled trials, involving fixed doses of ziprasidone, demonstrated a significant, linear, dose-response for mean changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores (in patients with baseline MADRS ≥14) ($P = 0.002$).[22]

Dosing

Ziprasidone is associated with a linear dose-response relationship; higher doses are associated with greater symptom improvement in patients with schizophrenia.[22,23,24]

- Pooled data from two similarly designed, 6-week, randomized, double-blind, placebo-controlled trials, involving fixed doses of ziprasidone, demonstrated a significant, linear, dose-response ($P\leq0.001$) in PANSS total score for ziprasidone doses between 40 and 160 mg/day compared to placebo; there was greater and more rapid improvement in psychopathology symptoms with Geodon daily doses of >120mg versus lower doses.[22,23]

- In a retrospective analysis of pooled data from three flexible-dose trials that compared ziprasidone 80 to 160 mg/day (all three trials) with olanzapine 5 to 15 mg/day (6-week trial), risperidone 6 to 10 mg/day (8-week trial), and aripiprazole 10 to 30 mg/day (4-week trial), higher ziprasidone doses were associated with greater efficacy in the treatment of schizophrenia and schizoaffective disorder.[24]

Ziprasidone initiated at higher doses improves symptoms in patients with schizophrenia and is associated with low discontinuation rates.[25,26]

- In a retrospective database analysis, patients initiating ziprasidone at higher doses (120-160 mg/day) displayed greater adherence to medication after 6 months compared with lower doses (40-119 mg/day; $P = 0.024$).[25]

- In a retrospective study using Maryland Medicaid claims data, a high initial dose of ziprasidone (120-160 mg/day) was associated with a lower risk of discontinuation (hazard ratio = 0.872; $P = 0.0045$).[26]

Switching from other antipsychotics

Switching to ziprasidone from conventional antipsychotics, risperidone or olanzapine results in short- and long-term improvement in positive and negative symptoms.[27,28,29]

- In a pooled analysis of three 6-week open-label trials, statistically significant improvements in overall psychopathology and negative symptoms were observed in patients who switched to ziprasidone (40-160 mg/day) from olanzapine or risperidone (all $P<0.05$, PANSS Total score, all $P<0.05$, BPRSd Total score, all $P<0.005$, negative symptoms improvement).[27]
- In a pooled analysis of three 52-week open –label extension studies of patients who initially completed one of the 3 identically designed 6-week open-label, parallel-group, multicenter studies, significant improvements from pre-switch baseline to study endpoint in CGI-S, PANSS total score, and PANSS negative symptom scale were observed in patients who switched to ziprasidone from conventional antipsychotics, olanzapine or risperidone (all $P<0.01$).[29]
- In a 26-week, open-label, multicenter trial, statistically significant improvement in PANSS total score was observed at 3- and 6-month endpoints (both $P<0.0001$) in patients who switched to ziprasidone from conventional antipsychotics, other atypical antipsychotics (olanzapine or risperidone), and the rate of remission (PANSS total <60) increased from 24.2% to 42.4% after 6 months of ziprasidone treatment.[18]
- In a 12-week, open-label, baseline-controlled, single-treatment, multicenter, flexible-dose study, patients switching from either haloperidol, olanzapine, or risperidone to ziprasidone showed statistically significant improvements in BPRS, PANSS total, PANSS positive subscale, PANSS negative subscale and CGI-S scores from baseline to Week 12 ($P\leq0.003$).[28]

Cognition

Ziprasidone is associated with short- and long-term improvement in cognitive function in patients with schizophrenia or schizoaffective disorder.[30,31,32,33,34]

- In a 6-week, randomized, multicenter, double-blind, parallel-designed trial, both ziprasidone and olanzapine significantly improved performance in attention (Trail-Making Test Part A [TMT Part A]) and memory (Ray Auditory Verbal Learning Test [RAVLT]) domains of cognitive function, with no significant differences in the level of cognitive enhancement between groups.[32] The results from the 6-month extension study demonstrated that ziprasidone and olanzapine were equally effective in maintaining enhancement of cognition. Based on a comparison of cognitive test scores with normative standards in the 6-month extension trial, a substantial number of patients in both treatment groups normalized their cognitive performance.[31]

- In an 18-week, multicenter, parallel-group, randomized, double-blind clinical trial, ziprasidone and clozapine produced comparable improvements in individual cognitive function in patients with schizophrenia with a history of either treatment resistance or intolerance to previous antipsychotics (e.g., statistically significant improvement in the ziprasidone group on the TMT Part B, the RAVLT trial 1 and the RAVLT total learning ($P<0.05$ versus baseline for all) and significant improvement on the RAVLT trial 1 and Stroop interference in the clozapine group ($P<0.05$ versus baseline for all).[33]

- In the 6-month extension of a 6-week open-label study in patients who switched to ziprasidone from conventional antipsychotics, olanzapine or risperidone, there were significant improvements from baseline to endpoint in episodic memory, attention, executive function, and letter fluency.[30]

Schizoaffective Disorder

Ziprasidone provides dose-related improvement in the treatment of schizoaffective disorder.[35,36]

- Data combined from two separate, randomized, double-blind, placebo-controlled trials demonstrate that ziprasidone (40-120 mg/day) offers dose-related improvement in schizoaffective symptoms based on BPRS total, BPRS core, BPRS manic subscale, and CGI-S scores ($P<0.01$).[35,36]

Treatment-resistant schizophrenia

In patients with treatment resistant schizophrenia, ziprasidone demonstrated efficacy comparable to chlorpromazine in short- and long-term treatment.[37,38]

- In a 12-week, randomized, double-blind, multicenter study, patients treated with ziprasidone 80-160 mg/day experienced comparable positive symptom improvement (BPRSd and PANSS total scores) and greater negative symptom improvement ($P\leq0.05$, CGI-S and PANSS Negative Subscale scores) compared with chlorpromazine 200-1200 mg/day.[37] In the 1-year, open-label extension of the 12-week trial, 74% of ziprasidone-treated patients maintained responder status, and patients who

switched from chlorpromazine to ziprasidone for the extension study showed significant mean improvement in PANSS Total Score ($P<0.05$), PANSS Negative Subscale ($P<0.01$) and anxiety-depression ($P<0.05$).[38]

Acute Bipolar Mania

Ziprasidone demonstrates rapid efficacy in mixed and manic subtypes of acute mania in patients with bipolar disorder, compared with placebo[39,40,41,42,43,44] or haloperidol.[45]

- In two pivotal, similarly designed 3-week, double-blind, placebo-controlled, randomized trials, ziprasidone (40-80 mg BID) treatment resulted in greater mean changes in symptom improvement compared to placebo (Mania Rating Scale (MRS) score: $P<0.05$ and $P<0.01$, respectively); significant improvements were observed from Day 2 onward for MRS and CGI-S scores (with the exception of MRS at Day 4).[39,40] In a pooled analysis of these two studies, significant improvement of symptoms were also observed by Day 2 in both studies with ziprasidone treatment (160 mg/day) in patients with acute manic or mixed episodes ($P<0.05$, $P<0.01$, respectively).[41]
- In a 12-week, double-blind, placebo-controlled trial, ziprasidone (40-80 mg BID) demonstrated equal ability to maintain treatment response compared with haloperidol (4-15 mg BID) in patients with bipolar disorder with current manic/mixed episodes.[45]

Ziprasidone showed improvement in depressive symptoms by Day 4 compared to placebo in dysphoric mania patients.[46]

- In a, pooled analysis of two 3-week studies, ziprasidone treatment (160 mg/day) provided significantly greater mean improvement in patients with dysphoric mania compared with placebo in depressive symptoms (Hamilton Depression Rating Scale [HAM-D] scores) beginning at Day 4 ($P = 0.026$) and continuing to the study endpoint ($P = 0.027$). Greater mean improvements in other symptom domains were also observed beginning at Day 2 (CGI-S and MRS scores) and Day 7 (PANSS total, PANSS positive, and GAF scores) and continuing to the study endpoint.[46]

Concurrent use of ziprasidone and lithium provides safe and rapid efficacy in patients with bipolar disorder.[47,48]

- In a 21-day, double-blind study in patients with bipolar I disorder, the mean change from baseline in SARS and BAS scores was significantly greater in the ziprasidone than placebo group ($P<0.05$); AIMS scores were comparable in both groups.[47]

Efficacy with Intramuscular (IM) Formulation

Agitation

Ziprasidone IM demonstrates rapid and well-tolerated improvement in the symptoms of acute agitation in schizophrenia, with a dose-related effect.[49,50,51,52]

- In a 24-hour, prospective, randomized, double-blind study, ziprasidone IM 20 mg reduced the symptoms of acute agitation (Behavioral Agitation Rating Scale [BARS], PANSS, CGI-S, CGI-I) in patients with psychotic disorders compared with ziprasidone IM 2 mg, with significant effects observed as early as 30 minutes (mean BARS score, $P<0.01$).[49]
- In a 24-hour, double-blind, fixed-dose study, IM 10 mg significantly reduced mean BARS score at all time points up to 4 hours except for 30 and 45 minutes ($P<0.01$) compared to ziprasidone IM 2 mg.[50]
- In an analysis from two 24-hour, double-blind, randomized, active-controlled studies, ziprasidone IM showed a significant dose-related effect (20 mg vs 2 mg) at 4 hours on the psychosis measures of the PANSS early psychosis factor score (4 hours, $P = 0.01$; 24 hours, $P = 0.006$) and on the PANSS positive subscale (4 hours, $P = 0.047$; 24 hours, $P = 0.032$).[51]
- In a 42-day, international, multicenter, randomized, open-label study, sequential IM to oral ziprasidone was superior to haloperidol in reducing hostility, showing evidence of an anti-hostility effect in the first week of treatment based on the hostility item from the BPRS; differences were maintained until Day 42, at which point the differences reached trend levels ($P=0.056$).[52]

IM to oral transition

Sequential IM and oral ziprasidone offer improvement in efficacy parameters with important tolerability advantages over haloperidol.[53,54,55]

- In a 7-day, randomized, open-label, parallel-group, multicenter study, ziprasidone IM significantly demonstrated greater improvement in mean reductions from baseline in BPRS total ($P<0.05$), BPRS agitation ($P<0.01$) and CGI-S scores ($P<0.01$), compared to haloperidol IM.[53]

- In a 6-week, multicenter, randomized, open-label study, improvement in efficacy during IM treatment with ziprasidone was sustained and increased through the transition to oral ziprasidone (BPRS, $P<0.0018$; BPRS negative subscale, $P<0.0001$).[54]

ZIPRASIDONE SAFETY/TOLERABILITY

Metabolic profile

Ziprasidone has a neutral effect on weight and metabolic parameters with some evidence showing improvements in metabolic parameter [29,56,57,58,59,60,61,62,63,64] thus potentially reducing associated risk of diabetes and coronary heart disease (CHD).[65,66]

- In the landmark 18-month, multicenter Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, sponsored by the National Institute of Mental Health, comparing four atypicals and one conventional agent for the treatment of chronic schizophrenia, only ziprasidone was associated with improvements in several metabolic parameters such as weight, lipids, and glycosylated hemoglobin, with no impact on prolactin.[57] In the CATIE Phase 2 trial, comparing the effectiveness of olanzapine, quetiapine, risperidone and ziprasidone in patients who had discontinued the atypical antipsychotic randomly assigned during Phase 1, ziprasidone was associated with a mean weight loss of 1.7 lbs/month whereas olanzapine, quetiapine, and risperidone were associated with weight gain.[58]

- In a post-hoc integrated analysis on data from 21 placebo- or active-controlled trials, ziprasidone was associated with an overall weight neutral profile compared to placebo, haloperidol, olanzapine, and risperidone; 57% of ziprasidone-treated patients' weight remained unchanged at 12 months.[62]

- In a pooled analysis of three 6-week open-label, multicenter trials in patients who switched to ziprasidone from olanzapine and risperidone, significant decreases were observed in body weight and body mass index (BMI) from baseline to study endpoint (switched from olanzapine: mean weight change –1.8 kg, $P<0.001$, effect size 0.616; BMI 31.7-31.1, $P<0.0001$, effect size 0.610; switched from risperidone: -0.86 kg, $P<0.02$, effect size 0.335; BMI 29.6-29.3, $P<0.02$, effect size 0.304).[56]

- In a pooled analysis of three 52-week open –label extension studies of patients who initially completed one of the 3 identically designed 6-week open-label, parallel-group, multicenter studies, duration of ziprasidone treatment was a significant predictor of weight loss for patients previously treated with either olanzapine or risperidone (all $P<0.01$). Improvements in body weight, BMI, cholesterol, and triglyceride levels were observed within 6 weeks of the switch to ziprasidone from olanzapine or risperidone, with improvements continued or maintained during the subsequent 52-week extension period.[29]

- In a 26-week, multicenter, observational, open-label switch study, significant reductions in body weight (-5.1 kg, $P<0.0001$), BMI (-1.7 kg/m^2, $P<0.001$), glucose levels (-14.1 mg/dL, $P<0.0001$), total cholesterol (-24.1 mg/dL, $P<0.0001$), LDL (-17.1 mg/dL, $P = 0.004$), and triglycerides (-46.2 mg/dL, $P<0.0001$) were observed in patients who switched to ziprasidone from olanzapine, risperidone, conventional antipsychotics, and other atypical antipsychotics.[59]

- In a pooled analysis of two similarly designed open-label, multicenter, 8-week, flexible-dose studies of ziprasidone, which differed by type of antipsychotic monotherapy prior to switch (haloperidol, risperidone, olanzapine or quetiapine), mean body weight significantly decreased from baseline to Week 8 after switching to ziprasidone from olanzapine, risperidone, and quetiapine.[60]

- Data from short-term (≤12 weeks), long-term (>12 weeks), antipsychotic switch core (6 weeks), and switch extension (46-52 weeks) studies for an "at risk" patient population demonstrated that ziprasidone therapy resulted in a significant improvement in triglycerides, total cholesterol, weight and BMI in patients with metabolic risk.[63]

- A post-hoc analysis of population from the CATIE phase 1 study that examined changes in metabolic syndrome (as defined by NCEP) status found that proportion of patients meeting metabolic syndrome criteria increased from baseline to Month 3 for olanzapine (from 34.8% to 43.9%), but decreased for ziprasidone (37.7% to 29.9%) (p=0.001).[64]

Diabetes and CHD Risk

- In a model that evaluated the expected 10-year risk of CHD and diabetes events for hypothetical populations of 10,000 men and women with schizophrenia, ziprasidone was associated with a lower risk of diabetes and CHD events compared with other atypical antipsychotics.[65]

QTc prolongation

Ziprasidone is associated with a degree of QTc prolongation.[1,57,58,67,68,69]

- During premarketing evaluation of ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received ziprasidone and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec.[1]

- In a rigorously controlled, Phase 1 study that showed similar QTc increase from all tested antipsychotics (thioridazine 300 mg/d, 30.1 msec; ziprasidone 160 mg/d, 15.9 msec; risperidone 6 mg/d, 3.9 msec; risperidone 8 mg/d, 3.6 msec; haloperidol 15 mg/d, 7.1 msec; quetiapine 750 mg/d, 5.7 msec; olanzapine 20 mg/d, 1.7 msec), no further QTc increases were observed with any agent with the presence of metabolic inhibition [inhibitors (antipsychotic): ketoconazole 400 mg + paroxetine 20 mg (haloperidol); ketoconazole 400 mg (ziprasidone and quetiapine); fluvoxamine 100 mg (olanzapine); paroxetine 20 mg (risperidone and thioridazine)].[67]

- In an randomized, open-label study that evaluated effects of oral ziprasidone on QTc at peak drug exposure at steady-state dose levels, ziprasidone 320 mg/day resulted in a marginal increase in mean QTc interval (3 msec) in comparison to ziprasidone 160 mg/day.[68]

- In a single-blind, randomized, multicenter study, magnitudes of increase in QTc at Cmax were comparable for ziprasidone IM (4.6 msec) and haloperidol IM (6.0 msec), with no patients experiencing a QTc ≥500 msec.[69]

- In both phases of the CATIE trial, there were no significant differences between ziprasidone and any of the other antipsychotics in mean change in QTc interval (olanzapine, 1.2 msec; quetiapine, 5.9 msec; risperidone, 0.2 msec, perphenazine, 1.4 msec; ziprasidone, 1.3 msec).[57,58]

Drug interactions

The distinctive pharmacokinetic profile of antypsychotics is an important determinant of safety, efficacy and adverse event profile when prescribing in the presence of potential metabolic inducers or inhibitors.

- Two enzymes, cytochrome P450 3A4 (CYP3A4) and aldehyde oxidase, are responsible for ziprasidone metabolism in humans. Because aldehyde oxidase is responsible for the majority of Geodon® metabolism, the potential for pharmacokinetic drug interaction with other drugs may be reduce.[70]

Indicated Dose Adjustment by CYP450 Enzyme

	1A2	2D6	3A4
GEODON	—	—	—
Abilify®	—	↑↓	↑↓
Seroquel	—	—	↑↓
Risperdal*	—	↑↓	—
Zyprexa*	↑↓	—	—

— no dose adjustment
↑ increase dose (inducer)
↓ decrease dose (inhibitor)

Individual product prescribing information.

*Product prescribing information suggests dose adjustments may be required.

- Ziprasidone is unlikely to cause clinically important drug interactions mediated by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[71]

OFF-LABEL USE

Note that Pfizer Inc does not suggest or recommend the use of Geodon in any manner other than as described in the Prescribing Information approved by the U.S. Food and Drug Administration (FDA).

Maintenance of bipolar disorder

Ziprasidone demonstrated rapid and sustained efficacy with no adverse effects on weight and lipid profile in the long-term management of patients with bipolar disorder.[41,72]

- In the 52-week extension of a 21-week acute mania study, ziprasidone-treated patients continued to show improvements in MRS and CGI-S scores that were significantly greater compared with baseline scores during the original 21-day study[41]; the efficacy of ziprasidone was maintained across all subtypes of acute mania (mixed, manic, psychotic, nonpsychotic).[72]
- A review from 5 trials (3 randomized, 21-day, placebo-controlled, double-blind trials; 2 open-label, 52-week extensions of the corresponding 21-day short-term studies, revealed that ziprasidone was generally safe and well tolerated, in patients with acute bipolar mania, with no adverse effects on weight and lipid profile.[43]

Bipolar Depression

Ziprasidone has shown potential efficacy and is well tolerated in the off-label treatment of bipolar depression.[73]

- In a 6-week, prospective, open-label study (N=10), ziprasidone augmentation (mean dose 84 mg/day) was shown to benefit patients with bipolar depression with a 34% decrease in mean MADRS rating, 50% treatment response (reduction in MADRS score), 40% remission rate (MADRS < 12), and a 33% decrease in mean BDI score. Improvement with ziprasidone augmentation in all measures was observed within the first week of treatment.[73]

Treatment-resistant depression

Ziprasidone has shown potential efficacy as adjunctive treatment and is well tolerated in the off-label treatment of treatment-resistant depression.[74,75]

- Results from a 6-week, open-label study (N=20) suggest that augmention of SSRI therapy with ziprasidone may be useful in treatment-resistant major depressive disorder; 62% of patients were classified as responders.[74]
- In a 6-week, open-label study followed by an 8-week, randomized, open-label continuation study (N=61), ziprasidone augmentation displayed greater improvement than continuing high-dose sertraline monotherapy in patients with treatment-resistant major depression, including a significantly greater mean change in CGI-S scores ($P<0.05$).[75]

Pediatric patients with Bipolar disorder, Tourette's syndrome and Autism

Ziprasidone has shown potential efficacy and is well tolerated in the off-label treatment of children and adolescents with bipolar disorder, Tourette's Syndrome, and autism.[76,77,78,79,80,81]

- In an 8-week, open-label prospective study, ziprasidone treatment was associated with a significant short-term improvement of symptoms of pediatric bipolar disorder (YMRS, $P<0.001$; CDRS-R, $P<0.001$; BPRS Resistance, $P = 0.02$; BPRS Positive symptoms, $P = 0.01$).[76]
- In a prospective, randomized, double-blind, placebo-controlled, multi-center, 4-week study ziprasidone was associated with statistically significant improvement over placebo on both the YMRS and CGI-S scales.[77]
- In an open-label, 26-week extension of study (DelBello 2008), the overall efficacy observed in the initial study was maintained with longer-term treatment (mean change in YMRS score from the end of the previous double-blind study to the end of this study using LOCF was -3.3 (95% CI, -4.98 to -1.57). Ziprasidone also demonstrated a neutral metabolic profile and was safe and generally well tolerated for long-term treatment of bipolar disorder in children and adolescents.[78]
- In a 56-day double-blind, placebo-controlled, randomized trial (N=28), results show ziprasidone (5-40 mg/day) may be effective in the treatment of Tourette's syndrome, with greater reductions in Global Severity ($P = 0.016$) and Total Tic ($P=0.008$) scores compared to placebo.[79]
- In a 6-week open-label pilot study (N=12) of patients diagnosed with autism, a LOCF analysis revealed that 75% of ziprasidone treated patients were considered to be treatment responders (rated as "much improved" or "very much improved").[80]
- In an open-label prospective trial assessing the electrocardiographic safety profile of low-dose ziprasidone (≤40 mg/day) among pediatric outpatients treated for 4.6±2.0 months (up to 6 months), statistically significant changes were observed from baseline to peak values in heart rate ($P<0.001$), PR ($P<0.001$), and QTc intervals ($P<0.01$), but not QRS complex width ($P=0.87$).[81]

ECONOMIC AND OUTCOME STUDIES

Cost-effectiveness studies

Ziprasidone therapy results in improved tolerability, lower total direct costs, and greater cost-effectiveness compared to other antipsychotics.[82]

- Based upon a Markov model that simulated a 4-armed, randomized, parallel-group, 1-year therapeutic course of a cohort of patients with chronic schizophrenia, ziprasidone treatment resulted in more time with controlled psychotic symptoms and lower expenditures for patient care as compared to olanzapine, risperidone, and haloperidol treatments (total months of symptom control: 9,960 vs. 9,930, 9,920, and 9,880, respectively; cost in USD: $18,002, 945 vs. $19,109,686, $18,920,507, and $18,085,813, respectively). In all instances where variables were modified, the sensitivity analyses showed that initiating treatment with ziprasidone continued to be less costly than initiating treatment with risperidone or olanzapine.[82]

Cross-sectional or retrospective cost studies

Ziprasidone provides longer persistence, better compliance, and greater decreases in psychiatric-related costs compared to other atypicals.[83]

- In a comparative analysis of medical and pharmacy claims, patients initiated on ziprasidone following a psychiatric hospital discharge exhibited longer persistance, greater compliance and significantly greater declines in mean annual psychiatric costs (-$6,866) than patients treated with olanzapine (-$3,353, $P = 0.0116$) or risperidone (-$4,764, $P = 0.0021$), with a reduction in hospitalizations being the main driver for cost savings.[83]

- In a model that evaluated the expected 10-year risk of CHD and diabetes events for hypothetical populations of 10,000 men and women with schizophrenia, ziprasidone treatment was associated with the lowest risk for diabetes and CHD compared with olanzapine, risperidone. Differences in the expected risk for coronary heart disease and diabetes resulted in substantially lower total estimated medical costs for ziprasidone relative to olanzapine, quetiapine, and risperidone.[65]

Ziprasidone added to a formulary as the preferred atypical antipsychotic reduces pharmacy costs.[84]

- In a retrospective analysis on pharmaceutical and drug costs to assess the economic impact of a formulary change specifying ziprasidone as the preferred atypical antipsychotic agent in inpatient psychiatric facilities, the addition of ziprasidone to formulary decreased medication ($82,257 before ziprasidone vs. $59,507 after ziprasidone, $P<0.001$) and pharmaceutical costs ($191,000 before ziprasidone vs. $135,000 after ziprasidone) as well as concomitant medication use (8% and 6% monthly reduction for anticholinergic agents and antidepressants, respectively).[84]

Quality of life studies

Long-term treatment with ziprasidone was associated with better remission rates and favorable effects on quality of life compared to haloperidol.[19]

- In a 40-week, randomized, double-blind core study followed by a 3-year double-blind continuation study, the proportion of patients in remission in the final 6 months was significantly higher in the ziprasidone twice daily (BID) group and the combined ziprasidone BID and QD groups vs haloperidol (40%, 38%, and 23%, respectively; $P<0.05$). Ziprasidone was associated with significantly better quality of life than haloperidol as improvement in remission status over time had a significant positive effect on QLS scores.[19]

Switching to ziprasidone from other antipsychotics improved cognitive performance and affective symptoms in patients with schizophrenia, which may contribute to enhanced prosocial functioning.[85]

- In a re-analysis of data from 270 patients switched from previous treatment with conventional antipsychotics, risperidone or olanzapine to ziprasidone 20-80 mg BID for 40 days, ziprasidone treatment improved PANSS prosocial subscale ($P<0.05$), which may contribute to enhanced prosocial functioning.[85]

OVERALL VALUE

Geodon provides proven efficacy in schizophrenia and acute bipolar, manic or mixed, episodes, with a well-established safety & favorable tolerability profile with neutral effects and in some cases improvement relative to other atypical antipsychotics on weight and metabolic parameters, key risk factors in the development of diabetes and heart disease.[86] Furthermore, Geodon when used at clinically effective doses has demonstrated greater treatment persistence relative to other atypical antipsychotics without increasing medical care utilization.[83] Geodon's favorable metabolic profile may benefit patients' long-term health in terms of greater potential reduction in risk for developing diabetes and heart disease relative to other atypical antipsychotics, potentially translating into meaningful economic benefits in terms of net health care cost reductions.[65]

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Pfizer Inc.
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Pfizer Medical Information Fulfillment Center
MS: 685-27-6A
New York, NY 10017

Worldwide Pharmaceuticals Operations

August 04, 2009

Tami Eide, PharmD
Idaho Dept. of Health and Welfare
PO Box 83720
Boise, ID 83720

Dear Dr. Eide

Your Medical Outcomes Specialist, Susan Heineman, has referred to Medical Information your request for information regarding Xalatan® (latanoprost). Pfizer Inc is pleased to provide you with the following information in response to your specific request. PLEASE NOTE that this information is intended only for the specific person who has requested information about a specific Pfizer Inc product. IF YOU DID NOT SPECIFICALLY REQUEST THE INFORMATION THAT IS INCLUDED, PLEASE DISCARD IT AND CALL 1-800-438-1985 TO REPORT THIS TO US.

The enclosed document contains relevant clinical and economic data for your review. Please keep in mind that this information was prepared with the understanding that it should not be disclosed to anyone other than those who in the course of their job responsibilities require access to the Executive Summary.

Xalatan Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Please refer to the package insert for complete prescribing information.

I hope this information is helpful. Thank you for your interest in Pfizer. Please contact Pfizer at 1-800-438-1985 to report an Adverse Event or if you have any other questions regarding Pfizer products. Licensed healthcare professionals may also log on to www.pfizermedicalinformation.com. Please take a few moments to let us know how we are meeting your needs by completing our survey via the web at http://survey.pfizermedicalinformation.com using the reference number listed below the signature at the end of this letter.

Sincerely,

Michael S. Rocco, PharmD
Director
Pfizer U.S. Medical Information

ROCCOM / 11474593

Encl.

Layout and/or size adjusted for ease of reading and printing

Xal-Ease™

PHARMACIA

Delivery aid for administering XALATAN® Ophthalmic Solution (latanoprost ophthalmic solution)

Before using your XAL-EASE™ delivery aid, read the complete instructions carefully.

PATIENT'S INSTRUCTIONS FOR USE

XAL-EASE holds one bottle of XALATAN and helps you deliver a drop of the medication into the eye(s).

Contents:
1. XAL-EASE™ delivery aid
2. Bottle cap opener

The supplies needed to use the delivery aid are shown in Figure 1.

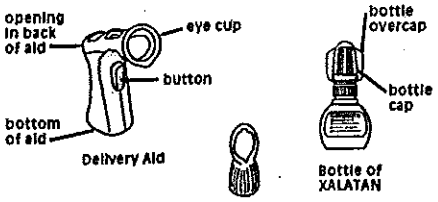

Figure 1

Preparing the aid for use

1. Before you administer the eye drops, wash your hands thoroughly with soap and water.
2. As shown in Figure 1, each bottle of XALATAN has two caps — a clear winged overcap and a turquoise bottle cap. Remove only the clear overcap from the bottle of XALATAN by slightly twisting it with your fingers so the overcap breaks away from the bottle.
3. Discard the overcap.
4. The turquoise bottle cap should remain on the bottle. Insert the bottle into the opening in the back of the delivery aid. Be sure the bottle is pushed fully into the delivery aid (Figures 2 and 3).

Figure 2

Figure 3

5. Turn the delivery aid so the turquoise cap on the bottle of eye drops is facing you.
6. Remove the cap from the bottle by unscrewing it with the bottle cap opener or with your fingers (Figure 4).

Figure 4

(continued)

Placing the delivery aid over the eye area

7. Tilt your head back.
8. Place the forefinger of your free hand at the top of your cheek and pull your lower eyelid down slightly. Using your other hand, place the eye cup of the delivery aid over the eye area so it rests on your skin.
9. Be sure your head is tilted back far enough so that the aid is directly over your eye. This will allow for proper delivery of the drop of XALATAN (Figure 5).

Figure 5

Administering the eye drops

10. When the eye cup is in place, look upward, and press the button until one drop is released from the bottle and enters the eye.
11. Promptly remove your finger from the button to avoid the release of additional drops (Figure 6).

Figure 6

Handling the aid following use

12. After removing the delivery aid from the eye area, replace the bottle cap using the bottle cap opener or your fingers.
13. The bottle of XALATAN may be left in the delivery aid for future use.

Cleaning the delivery aid

14. The delivery aid may be cleaned with mild soapy water and rinsed with warm tap water.

PATIENT'S INSTRUCTIONS FOR REPLACING AN EMPTY BOTTLE OF XALATAN

1. Remove the empty bottle of XALATAN by pushing the cap end of the bottle with your thumb or finger so the bottle comes out through the opening in the back of the aid (Figure 7).

Figure 7

2. Place a new bottle of XALATAN in the delivery aid as described before (see Preparing the aid for use) so it is ready to use for your next treatment.

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Xal-Ease

Xal-Ease

0819364000

PATIENT'S INSTRUCTIONS FOR REPLACING THE XAL-EASE™ DELIVERY AID

A date is printed on each delivery aid carton. The aid should be replaced when the date is reached or if it is not working properly.

To request a replacement delivery aid, or for answers to questions about its use, call Pharmacia & Upjohn Drug Information and Medical Services at 888.691.6813 or visit our website at www.xalatan.com.

Manufactured for: Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

By: Scandinavian Health Ltd.
Taipei, Taiwan, R.O.C.

September 2002 819 364 000

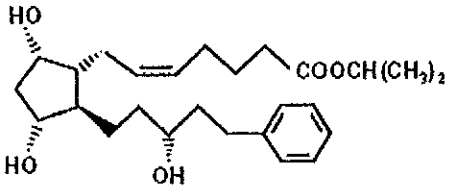
Xalatan®
latanoprost ophthalmic solution

0.005% (50 µg/mL)

DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:

M.W. 432.58



Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

XALATAN Sterile Ophthalmic Solution (latanoprost ophthalmic solution) is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of XALATAN contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. One drop contains approximately 1.5 µg of latanoprost.

CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics/Pharmacodynamics

Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Distribution: The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism: Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion: The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}$ =17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Animal Studies

In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris, with no proliferative changes observed. The change in iris color may be permanent.

Ocular administration of latanoprost at a dose of 6 μg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect was reversible upon discontinuation of the drug.

INDICATIONS AND USAGE

XALATAN Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CLINICAL STUDIES

Patients with mean baseline intraocular pressure of 24 – 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 –8 mmHg reductions in intraocular pressure. This IOP reduction with XALATAN Sterile Ophthalmic Solution 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of XALATAN once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase.

Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris

pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

XALATAN Sterile Ophthalmic Solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as XALATAN is administered. After discontinuation of XALATAN, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS

General: XALATAN Sterile Ophthalmic Solution may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see **WARNINGS**). Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with XALATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of XALATAN (see **WARNINGS**).

XALATAN may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

XALATAN should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. XALATAN should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is limited experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PRECAUTIONS**, *Information for Patients*).

Contact lenses should be removed prior to the administration of XALATAN, and may be reinserted 15 minutes after administration (see **PRECAUTIONS**, *Information for Patients*).

Information for Patients (see **WARNINGS** and **PRECAUTIONS**): Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XALATAN.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to

administration of the solution. Lenses may be reinserted 15 minutes following administration of XALATAN.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions: *In vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used they should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests.

Chromosome aberrations were observed *in vitro* with human lymphocytes.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2,800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XALATAN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse events referred to in other sections of this insert:

Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema (see **WARNINGS** and **PRECAUTIONS**).

Controlled Clinical Trials:

The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on XALATAN Sterile Ophthalmic Solution in the three 6-month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctuate epithelial keratopathy.

Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1 to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia.

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with XALATAN were upper respiratory tract infection/cold/flu, which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

Clinical Practice:

The following events have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include: asthma and exacerbation of asthma; corneal edema and erosions; dyspnea; eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); eyelid skin darkening; herpes keratitis; intraocular inflammation (iritis/uveitis); keratitis; macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; dizziness, headache, and toxic epidermal necrolysis.

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of large doses of latanoprost in monkeys has been associated with transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with latanoprost, bronchoconstriction was not induced. Intravenous infusion of up to 3 μg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 μg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

If overdosage with XALATAN Sterile Ophthalmic Solution occurs, treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop (1.5 μg) in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose as normal.

The dosage of XALATAN Sterile Ophthalmic Solution should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including XALATAN Sterile Ophthalmic Solution is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure lowering effect or cause paradoxical elevations in IOP.

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours

XALATAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

XALATAN Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 μg/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 μg/mL)
Package of 1 bottle NDC 0013-8303-04

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to the patient, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.

Rx only

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Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

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LAB-0135-8.0
Revised January 2009

XALATAN®
(latanoprost ophthalmic solution)

Executive Summary
12-Dec-2007

XALATAN® (latanoprost ophthalmic solution)
EXECUTIVE SUMMARY
December 12, 2007

Xalatan® (latanoprost ophthalmic solution) is a prostanoid selective FP receptor agonist that is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[1]

CLINICAL BACKGROUND AND BURDEN OF ILLNESS

Primary open-angle glaucoma (POAG) affects 2.2 million US individuals, a number that is expected to increase by 50%, to 3.36 million, in 2020 as the population ages.[2] POAG accounts for 50% to 66% of all glaucomas.[3] Because loss of visual field usually only becomes noticeable late in the disease course, it is estimated that less than 50% of affected patients realize they have the condition.[4]

Risk Factors

Race, Age, and Family History Influence the Risk of Developing POAG

Population-based studies have shown prevalence of POAG among blacks to be 3.4% to 5.6%[2, 5] versus 1% to 2% in whites.[6, 7, 8, 9] For populations aged 75 years or older, the prevalence of POAG increases dramatically to 4.7% among whites[8] and approximately 9% among blacks.[10] The prevalence of POAG in Hispanic populations ranges between the prevalence for whites and blacks.[11] Family history of glaucoma has been associated with a 5- to 20-fold increased risk for developing the disease, especially in older individuals.[12]

Burden of Glaucoma

A recent study by Lee et al[13] estimated that average direct treatment costs per patient per year ranged from $623 for glaucoma suspects or those with early-stage glaucoma to $2511 for patients with end-stage disease.

The National Eye Institute[14] estimates that blindness and visual impairment cost the federal government more than $4 billion each year in benefits and lost taxable income.

Patients with even mild visual impairment secondary to glaucoma may have difficulty with mobility, driving, socializing, working, and other daily activities.

DISEASE CHARACTERISTICS

The 2 main forms of glaucoma are POAG and primary angle-closure glaucoma (PACG). POAG and PACG both are characterized by damage to the optic nerve and visual field loss; however, they differ in terms of whether the trabecular meshwork is obstructed by the peripheral iris. In PACG, the iris obstructs the trabecular meshwork in the angle of the eye; in POAG, the trabecular meshwork seems to be open and unobstructed by the iris. This difference affects the medical and surgical management of the 2 forms of the disease.[15]

Age and elevated intraocular pressure (IOP) are the 2 risk factors for POAG most widely supported by evidence. A strong positive relationship has been demonstrated between elevated IOP and the progression to POAG, although the mechanism by which increased IOP contributes to POAG development and progression remains unclear.[16] Therapeutic reduction of IOP retards progression of visual field loss.[17] Other non modifiable risk factors associated with the development of glaucoma include cup-to-disc ratio, pattern standard deviation, and central corneal thickness. Although studies have shown a much higher prevalence of POAG in blacks, evidence suggests that black race in and of itself is not an independent risk factor for glaucoma progression but instead reflects a higher prevalence of risk factors such as thinner corneas, greater cup-to-disc ratios, and higher IOP levels in black individuals.[18]

Recent research suggests a continuum of glaucoma progression, with the earliest stages characterized by retinal ganglion cell apoptosis, or self-programmed cell death. With accumulating retinal ganglion cell damage or loss, cardinal signs of glaucoma appear in the retinal nerve fiber layer and in the optic disc, culminating in visual loss.[19, 20]

Some patients are at risk for rapid disease progression while others may live with the disease and remain asymptomatic for many years.

Clinical Presentation

Currently, the diagnosis of glaucoma is based on IOP levels, cupped appearance of the optic discs, and visual field defects.[21]

POAG is characterized by adult onset, is generally bilateral, and has a lack of obvious symptoms, especially in its early stages.[4]

Unfortunately, the measurement of IOP is not an effective or sufficient method for glaucoma screening. Individuals with glaucoma (eg, those with normal-tension glaucoma [NTG] as well as others) may have IOP levels that are consistently below 22 mmHg, the visual screening cutoff.[4] IOP is subject to cyclic fluctuations throughout the day and often peaks at a time when IOP is not routinely measured.[22]

In a healthy eye, IOP levels are maintained between 10 mmHg and 21 mmHg subject to diurnal variations.[23] Patients with elevated IOP (>21 mmHg) but no signs of visual field loss or pathologic cupping of the optic disc are classified as having OH.[24]

No single study is available to assess the impact of treatment on the risk of progression from OH to blindness. However, Weinreb et al[25] developed a model for estimating the global risk of disease progression in patients with OH and for calculating the number needed to treat to prevent progression to blindness. According to this model in untreated patients the estimated risk of progression from OH to unilateral blindness is 1.5% to 10.5% over 15 years and in treated patients the risk is 0.3% to 2.4%.[25] A comparison of the risk rates of the minimum and maximum values in this range, respectively, shows a relative risk increase for progression to blindness from OH that is approximately 4.4 to 5.0 times greater for untreated patients compared with treated ones.

Although practitioners can predict a likelihood that their at-risk patients will progress from OH to glaucoma, which, if left untreated, may ultimately lead to blindness, they do not know how quickly this progression will occur. Thus, treatment intervention should take place as early in the disease continuum as possible when OH is identified in patients with an elevated risk of progression.

Treatment Options

There is no treatment to reverse the optic neuropathy and the resultant visual field loss associated with POAG. Therefore, the current approach to treatment focuses on reducing IOP, the only modifiable risk factor.[19,26] The targeted IOP level differs among patients but is based on current damage to the optic nerve and the IOP level at which the damage occurred.[26] Therapeutic reduction of IOP delays progression of visual field loss even in patients with NTG, suggesting that some patients have heightened susceptibility to IOP levels usually considered normal.[17] IOP-lowering medications can reduce IOP by (1) decreasing the amount of aqueous humor produced by the ciliary body; (2) increasing aqueous humor outflow through the trabecular meshwork; or (3) increasing aqueous humor outflow through the uveoscleral pathway. Topical ocular medications used in the management of POAG act on 1 or more of these mechanisms to lower elevated IOP to a target pressure.[26]

American Academy of Ophthalmology (AAO) guidelines[4] advocate a 20% to 30% reduction of initial IOP; a targeted reduction of 40% or more is justified in the presence of severe, rapidly progressing optic nerve damage, excessively heightened IOP, and other risk factors such as family history or being of African-American ancestry. The AAO[4] grades the severity of glaucoma as follows:

- Mild: Characteristic optic nerve abnormalities are consistent with glaucoma but there is a normal visual field
- Moderate: Visual field abnormalities are in 1 hemifield and not within 5° of fixation
- Severe: Visual field abnormalities are in both hemifields or loss is within 5° of fixation

In the Ocular Hypertension Treatment Study,[27] the use of IOP-lowering topical ophthalmic agents reduced the relative risk of developing POAG by 60%. In individuals with elevated IOP, a 20% IOP reduction from baseline achieved by topical medical therapy may delay or prevent the onset of POAG over the course of 5 years. Nonpharmacologic treatment options include laser trabeculoplasty and trabeculectomy.

Mainstays of topical pharmacologic treatment to reduce IOP have included cholinergic agents, such as pilocarpine, that increase outflow of the aqueous humor but are associated with serious ocular side effects. Topical beta-blockers, which reduce aqueous humor secretion, have been another mainstay but have cardiovascular and respiratory side effects—particularly in elderly patients.[28]

Newer therapies include topical carbonic anhydrase inhibitors (CAIs), such as dorzolamide and brinzolamide that reduce aqueous secretion and are effective in lowering IOP. Oral CAIs, such as acetozolamide, have limited long-term use because of their systemic side effects.[28]

Topical alpha-2 adrenergic antagonists, such as brimonidine, also provide IOP-lowering treatment; however, these drugs can cause local allergic reactions.[28] They are useful in preventing the rise in IOP that can follow cataract surgery.

The Place and Anticipated Uses of Xalatan Therapy in the Treatment of Glaucoma

With the introduction of Xalatan® (latanoprost ophthalmic solution) in 1996, prostaglandin (PG) analogs have played an increasingly important role in the first-line therapy of glaucoma. In a number of comparison studies, PG analogs have demonstrated better results in lowering IOP relative to other topical therapies.[29] Xalatan has been indicated for first-line treatment of elevated IOP based on long-term safety studies since 2002.[30]

For efficacy of IOP reduction, Xalatan has been shown to be equivalent or superior to timolol and is equivalent to the other PGs. However, actual effectiveness in clinical practice is influenced by many other factors including persistence (time remaining) on therapy, which is, in turn, affected by such factors as physician satisfaction with IOP control, patient tolerability of the medication, concern with systemic effects, and convenience of the dosing schedule. The published evidence demonstrates that efficacy of Xalatan in the clinical trial is most likely to translate into effectiveness in the clinical setting.

CLINICAL EFFICACY

Earlier pivotal, 6-month, phase III clinical studies have shown once-daily Xalatan to be significantly more effective than twice-daily timolol in reducing diurnal IOP.[31] In fact, in these trials, while the IOP-lowering effect after 2 weeks of treatment was maintained for timolol, Xalatan yielded further significant reductions from 2 weeks to 6 months. Moreover, open-label extensions of these pivotal studies demonstrated that the reductions in IOP attained with Xalatan therapy persist for at least 24 months.[32, 33] Additionally, the long-term safety and efficacy of latanoprost was demonstrated in a 5-year study evaluating adjunctive latanoprost (3-year open-label with 2-year extension phase) in patients whose IOP was uncontrolled while using another IOP-reducing therapy.[30]

- Xalatan monotherapy has been compared with monotherapy with the PG analogs bimatoprost and travoprost in several multicenter, randomized, controlled studies. One key study by Parrish et al[34] compared efficacy and tolerability across all 3 PG analogs. In this study, Xalatan, bimatoprost, and travoprost were found to be equally potent IOP-lowering treatments that generally were well tolerated systemically. In the only other 3-way comparative study, Orzalesi et al[35] noted that mean IOP reductions were similar after the 3 PG analogs, and none of the differences among treatments reached statistical significance.
- The results of these 2 3-way comparative studies and the independent meta-analysis by van der Valk et al[29] suggest that the IOP-lowering ability for these agents in patients with POAG is comparable with no statistically significant differences and certainly no clinically significant differences.
- Despite reports of differences between agents at selected times of the day, when overall diurnal performance is tested, the PG agents each provide excellent IOP reduction.

Cost-Effectiveness

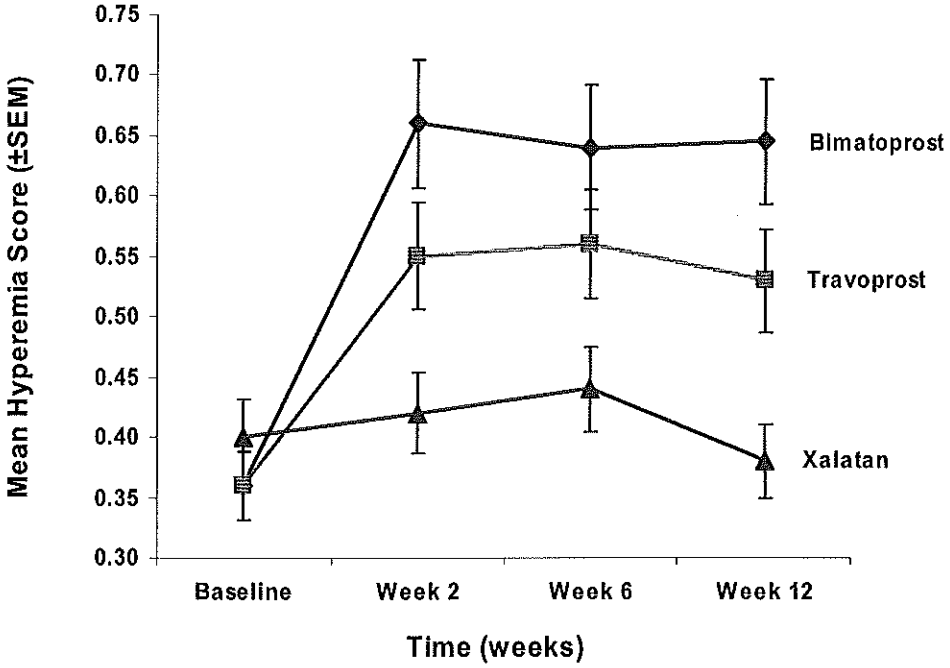
A recent model developed by Taylor et al[36] compared the effectiveness and costs of Xalatan with bimatoprost and travoprost when factoring in IOP reduction from clinical trials with persistence on therapy observed in a managed care database. After 1 year, Xalatan provided more days of IOP control (210 days) than did bimatoprost (190 days) or travoprost (191 days). After 3 years, Xalatan also provided more days of IOP control (570 days) than did bimatoprost (509 days) or travoprost (515 days). On average, latanoprost was least expensive over 3 years (latanoprost: $2267; bimatoprost: $2334; travoprost: $2287).

A 2005 study by Reardon et al[37] found greater cost-effectiveness, as measured by the expected cost per persistent day, for users of Xalatan 2.5 mL ($5.64) than for users of travoprost 2.5 mL ($7.28), bimatoprost 2.5 mL ($7.62), or bimatoprost 5 mL ($7.71). Despite additional consumption of Xalatan by patients in the first year due to greater persistence, approximately 50% of this marginal expense was estimated to be returned to the plan in medical cost offsets primarily due to fewer required medical visits to establish IOP control after changing therapies. Other benefits to the health plan from greater adherence, such as slowing disease progression and reducing glaucoma-related events such as higher rates of falls, were not included in these estimates.

CLINICAL SAFETY

In a 12-week, 3-way comparison of Xalatan, bimatoprost, and travoprost, Parrish et al[34] found that Xalatan demonstrated greater tolerability. There were fewer Xalatan-treated patients (53.7%) who reported an ocular adverse event versus bimatoprost-treated patients (73.7%) or travoprost-treated patients (64.5%) (P=.003 for the difference among the 3 treatments; P<.001 for the Xalatan-bimatoprost comparison). The most commonly reported ocular adverse event was conjunctival hyperemia (Figure 1). Patients on bimatoprost and travoprost had higher rates and more severe hyperemia; hyperemia was not transient and appeared throughout the duration of the trial. In addition, Parrish et al[34] found a significantly greater proportion of patients in the bimatoprost group (68.6%) reported overall adverse events than did those in the Xalatan group (51.5%) (P<.001).

Figure 1. Hyperemia Scores in a 12-Week Study*



*Based on physician assessment of hyperemia using standard photographs.
P=.001 for Xalatan versus bimatoprost at weeks 2 and 12.
SEM=standard error of the mean.
Parrish RK et al.[34] *Am J Ophthalmol* 2003;135:688-703.

In a comparative study by Gandolfi et al,[38] both Xalatan and bimatoprost were well tolerated, with a low incidence of adverse events. Conjunctival hyperemia, however, occurred more frequently with the use of bimatoprost than with Xalatan (36.1% vs 14.2%; $P \leq .001$). In a study by Netland et al,[39] less hyperemia also was reported in Xalatan 0.005% users (27.6%) than in patients using travoprost 0.0015% (38.0%) or 0.004% (49.5%).

The most common reported systemic adverse events seen with Xalatan were upper respiratory tract infections/cold/flu, which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1 to 2%.[1]

PERSISTENCY

Persistency, the continuous use of a drug over time, reflects patient-related factors such as drug tolerability and satisfaction as well as cost and can be a surrogate for successful treatment. More than a dozen studies have demonstrated that Xalatan provides consistently high persistency rates when compared with other ocular glaucoma treatments

- In a large retrospective, 12-month study of more than 28,000 managed-care prescription claims, patients (75% ≥65 years) treated with Xalatan as first-line therapy were significantly (P<.001) more persistent than those who received first-line beta-blocker (timolol, betaxolol), brimonidine, dorzolamide, or other PG analog therapy (travoprost or bimatoprost); the likelihood of initial therapy discontinuation was 37% greater for timolol, 72% greater for bimatoprost, and 58% greater for travoprost compared with Xalatan.[40] A 2-year study by Diestelhorst et al[41] also found greater persistency for Xalatan versus beta-blocker therapy.
- Reardon et al[42] found that, compared with Xalatan, those treated with bimatoprost were 38% more likely to discontinue therapy and 31% more likely to discontinue or change therapy while patients treated with travoprost were 36% more likely to discontinue therapy and 29% more likely to discontinue or change therapy (P<.001 for each comparison).

- A 1-year study by Nordstrom et al[43] found a significantly greater persistence rate for Xalatan (153 days) than for bimatoprost (106 days) or travoprost (108 days) (P<.0001).
- For patients who successfully returned for a refill after initiating a PG, Wilensky et al[44] found 1-year persistence percentage rates roughly equivalent at 1 year for Xalatan (69.4%), bimatoprost (68.1%), and travoprost (70.6%). When viewed in the context of the body of persistence research, this may indicate that patients who fail to persist on therapy may likely have problems with persistence early in the therapeutic course.
- In a study of data from the Glasgow Royal Infirmary, Montgomery and Mychaskiw[45] compared the frequency and reasons for changes in pharmacotherapy in the treatment of glaucoma and OH. Among 745 patients studied, there were 2049 changes in medication during the study period. The most frequent reason for change in medication regimen was failure to reach target IOP (29%) followed by adverse events (20%). Of the 3 PG analogs included in the study, Xalatan monotherapy had the lowest change rate (8.4%) compared with bimatoprost (13.9%) and travoprost (14.7%).

Persistency in the Medicare Population

A study by Schwartz et al[46] examined whether patients of Medicare age (65 and older) are as persistent with PG therapy as are younger patients aged 20 to 64. Data were reviewed from a managed care database on people who began therapy with either Xalatan, bimatoprost, or travoprost between April 1, 2001, and June 1, 2002. Of 4356 patients included in the study, 74% of the patients were aged 65 or older, reflecting the majority age of adults who use PG therapy. The study's authors found that patients of Medicare age were as persistent with PG therapy as were other age groups, with greater persistence seen for all patients using Xalatan compared with the other PG options.

SUMMARY

Together, the effectiveness, tolerability, and persistency demonstrated for Xalatan in controlled studies portray an agent with optimal drug utilization features in a variety of populations, including elderly Medicare populations, suggesting this agent is a logical option for the management of glaucoma and OH in cost-conscious managed care.

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